Cleveland Clinic Quarterly

A Bulletin Published by

The Staff of the Cleveland Clinic

CLEVELAND, OHIO

Vol. 8 OCTOBER, 1941 No. 4

CONTENTS

CLEVELAND CLINIC QUARTERLY

Issued in four numbers during the year; one in January, one in April, one in July and one in October, by Cleveland Clinic Foundation, 2020 East 93rd Street, Cleveland, Ohio.

Entered as second-class matter March 4, 1935, at the Post Office at Cleveland, Ohio, under the Act of August 24, 1912.

THE FRANK E. BUNTS INSTITUTE

announces

A Course in

PROGRESS IN THERAPY

on

MONDAY and TUESDAY

DECEMBER 1 and 2, 1941

and

A Course in

DISEASES OF THE EYE, EAR, NOSE AND THROAT

on

MONDAY, TUESDAY and WEDNESDAY

DECEMBER 8, 9, and 10, 1941

★

Description of the course in PROGRESS IN THERAPY, and an outline of the subjects to be covered may be found on page 257.

For further information regarding the courses in DISEASES OF THE EYE, EAR, NOSE AND THROAT, outline of subjects and application blanks, address A. D. Ruedemann, M.D., Cleveland Clinic, Cleveland, Ohio

MENSTRUAL EDEMA WITH INTRACRANIAL HYPERTENSION (PSEUDOTUMOR CEREBRI)

Report of a Case

E. PERRY McCULLAGH, M.D.

Within the past few years considerable interest has arisen in the occurrence of edema associated with the menstrual period. Such edema varies from a complaint of "puffiness" which may arouse mild passing interest of the clinician, to gross visible edema of as much as 14 pounds, perhaps, associated with severe papilledema and markedly increased cerebrospinal fluid pressure.

In 1928 Eufinger and Spiegler[1] observed some gain in weight at the menstrual time in 47 per cent of their subjects. Okey and Stewart[2] found 1 to 3 pounds increase in weight at the menstrual time in 5 of 20 women subjects, and Sweeney[3] reported a gain of 3 pounds or more in weight, usually premenstrually, in a third of 42 healthy young women studied. In 1933 Thomas[4] reported 2 cases of massive menstrual edema. In his first case there was a gain of as much as 12 pounds in weight, associated with headache, blurred vision and vomiting, and a previous history of arterial hypertension and albuminuria during pregnancy. In his second case no significant antecedent illness was noted and kidney function tests were normal. The menstrual periods were associated with an increase of as much as 14 pounds in weight, severe headache, "marked choking of the discs" and "markedly increased" spinal fluid pressure. In the case reported by Atkinson and Ivy[5] in 1936, there was marked edema of the feet and legs associated with the menstrual periods. In their case there was no evidence of abnormal serum protein levels nor of impaired renal function. Judging from the frequency with which a similar, although usually milder, picture is seen in clinical practice, this phenomenon must not be rare.

Premenstrual edema in reported cases has been associated with such symptoms as a sense of "puffiness", nervousness, emotional instability, numbness and tingling of the extremities, dizziness, unsteady gait, blurred vision, diplopia, dulled mental reactions, headache, and vomiting. All symptoms usually are aggravated a week to ten days preceding the onset of the menstrual flow.

In the title of this report, the term "pseudotumor cerebri" has been used for the purpose of calling attention to the fact that cases of this kind may be mistaken for cerebral neoplasms. The term "pseudotumor cerebri" is a broad classification, and in general, refers to cases presenting clinical symptoms and signs of intracranial tumor which, after complete study, are shown to have none. Such terms as "serous

meningitis" (Quincke, 1897[6], Davidoff and Dyke, 1936[7]), "serous effusions" (Warrington, 1914[8]), "otitic hydrocephalus" (Symonds, 1931[9]), and "toxic hydrocephalus" (McAlpine, 1937[10]) have been used to relate to conditions, some of which may be similar. The type of cases usually included under the term pseudotumor cerebri which are somewhat similar to the case reported here, are those of cerebral edema such as reported by Sahs and Hyndman[11]. Their cases are more nearly like some previously called "toxic or otitic" hydrocephalus. Three of their five cases occurred in children. All had fever, and one had an antecedent mastoiditis. In these latter respects they differ from such cerebral edema as is clearly associated with the menstrual cycle. Such cases as those of Sahs are similar to the ones reported by Gardner[12] in which increased venous pressure within the skull followed sinus thrombosis. The mechanism involved in such cases appears to be different from that present in the case reported here.

REPORT OF A CASE

The patient was referred to me by Dr. J. W. Schoolnic of East Liverpool, Ohio, and came for study on February 16, 1940. She was a 24 year old married, white, woman. Her chief complaints consisted of headache which had been present for five years and was increasing in severity; and within the preceding three weeks, diplopia.

The headaches were severe, generalized, "pounding" headaches associated with a sense of nervousness, faintness and mild giddiness, but no true vertigo. It was established, to our complete satisfaction, that they preceded a thyroidectomy (to be described below) by at least two years. Headaches occurred once or twice a month, as a rule, and varied in duration from one day to as long as three weeks. They usually appeared between ten days preceding and ten days subsequent to the first day of menstrual flow.

Beginning in December, 1939, she noted a sense of pressure in the head and a "gushing" noise in the right side of the head which seemed to be synchronous with the pulse. For three weeks before admission she had noted shadows shifting across the visual field. The diplopia was mild and had been continuous except for two days during a three-week period.

In 1936 she had had a right sided purulent otitis media, for which myringotomy was done. Contact with the physician who attended her at that time has established that there was no evidence of lateral sinus thrombosis.

On November 11, 1937, thyroidectomy was performed elsewhere for symptoms very similar to those present on admission to the clinic. Her symptoms were not relieved. Shortly after this operation puffiness of the eyelids developed, along with paresthesiae of the hands, a reduction in energy, dryness of the skin and brittleness of the nails. It has always been possible to control these symptoms by taking desiccated thyroid, which she has used irregularly since that time. Basal metabolic rate determinations were not done before thyroidectomy. In April, 1938, the basal metabolic rate was minus 29 per cent. She had taken desiccated thyroid (Lilly) in doses of 1½ grains per day following that finding. This dose was sufficient to cause a disappearance of the dryness of the skin and nails and was followed by loss of weight, but in spite of this the headaches and related symptoms continued to become more severe. On January 26, 1940, when the headache had been severe, the basal metabolic rate was minus 1 per cent. On that date thyroid medication was stopped. On February 11, the basal metabolic rate was minus 16 per cent.

The patient had had the childhood diseases without complications, and three years previously an only pregnancy ended in abortion. History of the special systems

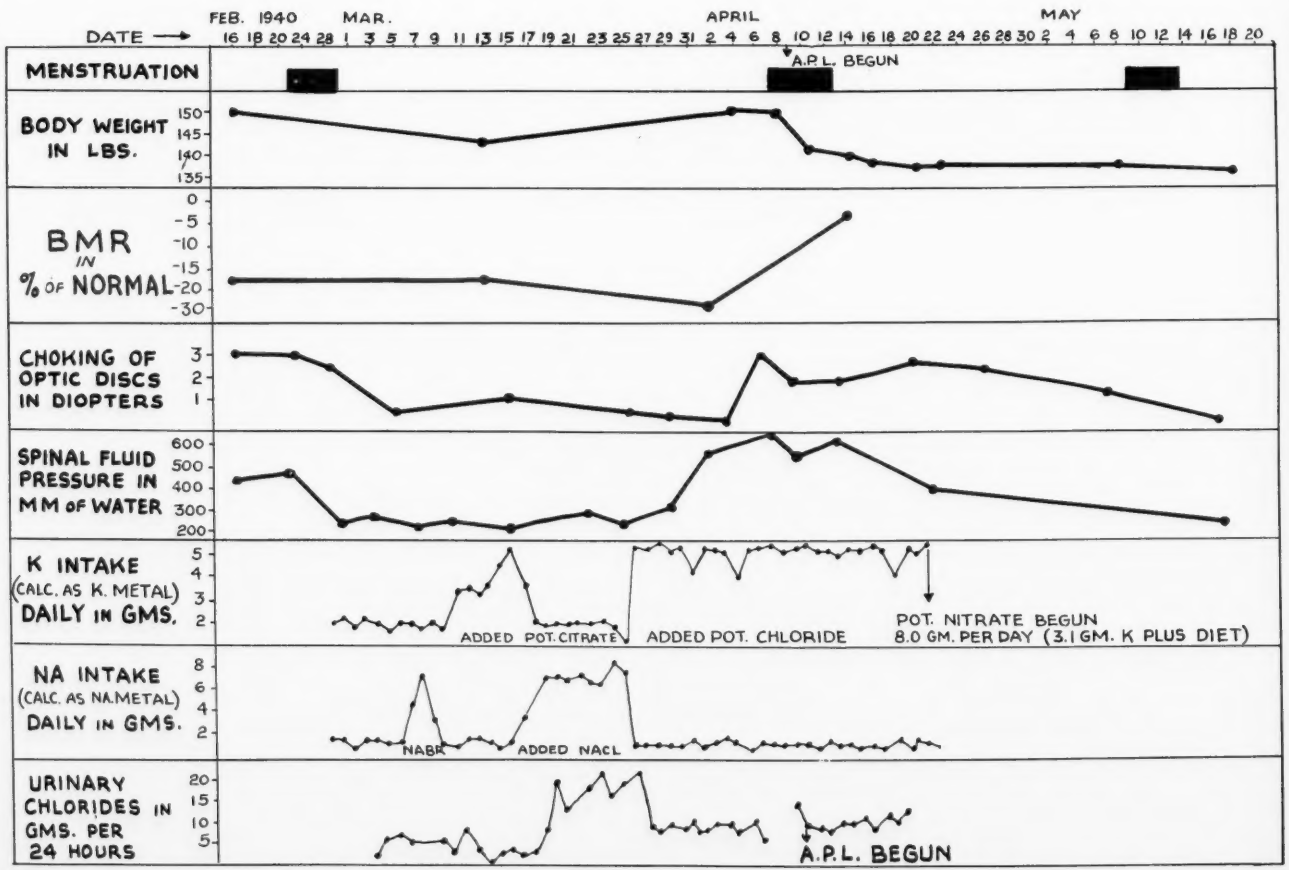


FIGURE 1: Showing variation in certain factors in the course of menstrual edema and lack of response to administration of certain electrolytes.

revealed nothing of importance. The menarche occurred at the age of 10½ years, and the menses had always been regular within a few days, occurring about every twenty-eight days and lasting from five to seven days.

No history suggestive of allergic reactions could be established. A slight elevation of temperature existed for two or three days following encephalography, but apart from the history of otitis media, no fever was known to have been present and there was none while she was under our observation. There was no history suggestive of encephalitis.

Physical examination revealed a rather short, stout, slightly pale young woman who was agitated and emotional and wept frequently. Her face looked mildly edematous. Her height was 63½ inches, and weight clothed 150 pounds. Her temperature was 99.2° F., pulse rate 84, and blood pressure 130 mm. systolic and 94 mm. diastolic.

The skin was rather dry. The pupils were equal, regular and reacted normally. There was 3 diopters of papilledema bilaterally, and perimetric fields showed bilateral enlargement of the blind spot. Extra-ocular muscle movements were normal. The oral hygiene was good. There was no lymphadenopathy. The thyroidectomy scar was in good condition and thyroid tissue was palpable on both sides of the neck. No abnormality of the heart, chest, abdomen or pelvis was noted. Neurological examination showed a suggestion of right facial weakness. Deep reflexes were hyperactive, but equal in the arms and legs; superficial reflexes were normal and no abnormal reflexes were found.

On February 19, 1940 the spinal fluid pressure was found to be 450 mm. of water. At that time Dr. A. T. Bunts made a ventriculogram which showed the ventricles to be normal in size and contour. Because the ventriculogram showed no cause for the increased intracranial pressure, it was decided that an encephalogram should be made. Immediately following the first procedure all obtainable cerebrospinal fluid was removed from the lumbar subarachnoid space, there being 75 cc. present. This was replaced by 85 cc. of air. Roentgenograms showed, in addition to normal ventricles, normal filling of the basal cisterns and cortical subarachnoid pathways. During the course of study, lumbar puncture was performed seventeen times. The cerebrospinal fluid was always under increased pressure, but it varied greatly, as is shown on the accompanying chart (Fig. 1).

Certain blood examinations are shown in Table 1. Blood chemistry studies were done on fasting blood unless otherwise stated.

Other laboratory data were as follows: Urinalysis, repeated at intervals on nine occasions, showed no abnormalities. The specific gravity was found to be as high as 1.029 and 1.032 on various occasions. The pH ranged from 5.5 to 7.5.

The blood volume was normal on March 11, 1940. On that day her spinal fluid pressure was also virtually normal. This test was not repeated when the spinal fluid pressure was high. The Wassermann and Kahn tests of the blood and spinal fluid were negative. The high levels of blood sodium are worthy of comment. In our laboratories, levels of blood sodium on normal individuals range commonly as high as 360 mg., but levels as high as those found in this case are not ordinarily seen.

Estrogen assays were done on March 3 and 7 on 24-hour specimens of urine; the first contained between 10 and 20, and the second less than 10 rat units, according to the method of Gustavson and D'Amour[13].

Urinary androgens were estimated by the capon method of McCullagh and McLin[14], and were 14 international units on March 2.

The spinal fluid protein on several occasions varied between 30 and 35 mg. per 100 cc. There were no cells and no globulin. On each of ten occasions the amounts of various electrolytes in the spinal fluid were determined, and no variation in them was found which appeared to be related to the shifts in the patient's weight, papilledema and spinal fluid pressure. The calcium varied from 5.2 to 5.8 mg. per cent; the phosphorus was 1.2 throughout; the chlorides were between 643 and 695 mg. per 100 cc. on all occasions but one. Sodium was between 373 and 398 mg. This showed some tendency to be higher at the times when the cerebrospinal fluid pressure was high, but the shift of both sodium and potassium levels were not of sufficient extent or consistence to be definitely significant. (Table 2).

TABLE 1
BLOOD COUNTS AND CHEMISTRY

Date	*2/16/40*	*2/21/40*	*2/28/40*	*3/4/40*	*3/7/40*	*3/11/40*	*3/26/40*
Red blood cells	4,400,000					5,140,000	
White blood cells	5,300					6,600	
Hemoglobin	84%					91%	
Volume						3,816 (26 cc. cells per Kg.)	
Sugar	85 mg. (1 hr. p.c.)						
Cholesterol					222 mg.		
Calcium	10.3 mg. 4½ hrs. p.c.)				10.3 mg.		9.8 mg.
Phosphorus	3.2 mg. 4½ hrs. p.c.)				4.0 mg.		
Chlorides		462 mg.	561 mg.				
Sodium		384 mg.	382 mg.				
Potassium		17.5 mg.	21.3 mg.				
Proteins				7.9%			
Albumin				5.9%			
Globulin				2.0%			

TABLE 2
Sodium and Potassium Levels of the Cerebrospinal Fluid

Date	*Sodium mg./100 cc.*	*Potassium mg./100 cc.*
February 28	394	11.0
March 6	387	8.5
14	387	10.2
25	398	10.5
29	398	9.1
April 1	391	8.8
5		10.2
17	373	10.0

FIGURE 2: April 2, 1940, showing the facial edema present. The hair had been cut in preparation for surgery. Photograph taken during a menstrual period.

The hospital stay lasted until April 18, 1940, a period of 63 days. Throughout most of this time it was necessary frequently to use aspirin, phenacetine and codeine for headache. Occasionally morphine or Pantapon were necessary for pain, and barbiturates frequently were prescribed as hypnotics.

The course of some of the important factors in this case as they changed during her hospital stay are presented graphically in the accompanying chart (Fig. 1).

Thyroid medication was withheld until March 28. It should be noted that the symptoms had increased steadily previous to her admission and were severe up to January 26, when the basal metabolic rate was minus 1 per cent. Subsequently, following the menstrual period in February there was a striking fall in spinal fluid pressure, during which time no desiccated thyroid was being given. These facts, together with the consideration that the symptoms preceded thyroidectomy, make it appear most unlikely that the subsequent fall in intracranial pressure was due to thyroid medication. Desiccated thyroid was begun in doses of 2 grains per day on March 28, 1940 and has been continued.

During the hospital stay, an attempt was made to control the intake of certain electrolytes and water. The food was weighed to the fraction of a gram and the electrolyte content was calculated. This was difficult in itself although some degree of success was attained. It was clearly recognized that the level of sodium and chlorides still remained too high to be expected to cause diuresis in itself. The water intake, however, was

FIGURE 3: August 18, 1941. Photograph taken during a menstrual period.

inconstant, the patient behaving for most of the time very unlike a guinea pig and much more like a human female. The urinary output was measured as accurately as possible, but showed no clear correlation to the rise and fall of spinal fluid pressure and body weight. The lowest urinary volumes were 600 to 900 cc. March 2 to 7, whereas amounts of 2000 were found on March 22 and 24; 1900 on April 1; and 2100 and 2000 on April 5 and 6 respectively.

When the potassium intake was first increased, as shown on the chart, it was suspected that this might be capable of maintaining the low levels of spinal fluid pressure which were observed or of depressing them further. We attempted to test this by changing to a low potassium, high sodium intake, but no significant effect was seen. Following this the potassium was again increased to high levels by adding potassium chloride. It was apparent that this too had little effect for the spinal fluid pressures rose during its administration to the very high levels shown. On March 31 after preoperative orders had been written and subtemporal decompression seemed imminent, it was urged that observation be extended beyond one more menstrual period. We then wondered whether the chloride ion might be the important one, or whether the shift was due to other factors associated with the menses. The same dose of potassium chloride was therefore maintained until the menstrual flow began and during the time it was being given there was a striking fall in spinal fluid pressure and in body weight, amounting to ten pounds in eight days. On April 17 the potassium chloride was discontinued and potassium nitrate in doses of 8 grams per day was substituted. The spinal fluid pressure had already fallen from 610 mm. to 300 mm. of water.

On April 9, 1940, A. P. L. (Ayerst) was begun on the basis of improvement reported in Thomas'[4] case mentioned above. If any medication can be said to have influenced the course of this disease, it was A. P. L. It was continued from that time until June, 1941, as shown below. For most of the time it was used in conjunction with a low sodium diet, desiccated thyroid in doses of 2 grains daily; potassium nitrate, 6 to 8 grams per day was continued for many months. When the potassium nitrate was first discontinued in June, 1940, the symptoms recurred, A. P. L. having been reduced at the same time. Later, it was apparent that the symptoms were very well controlled without the use of potassium nitrate, provided adequate doses of A. P. L. were given.

Date	*A.P.L. Daily in international units*	*Potassium nitrate orally in grams per day*	*Progress*
4/9/40	600		
4/17		6.0	
4/23	500	8.0	
5/2			Menses began
5/3			Papilledema, 1 to 2 diopters
5/13	500	8.0	Discs hazy. Spinal fluid pressure 230 mm.
6/3	500	8.0	
6/4		8.0	Menses began
6/6	250	Discontinued	Optic fundi normal
6/15			Headaches recurred and becoming severe. Face puffy.
7/3	500	8.0	Menses. Visible edema
8/1	Discontinued	8.0	Fundi marginal blurring. Menses. No edema. Remained well until menses in September, when edema and headache recurred.
9/26	250 alternate days	Discontinued	Fundi normal
10/–	250 daily begun	Discontinued	Edema and headache 10 days premenstrual.
11/8	250	Discontinued	Menstrual period symptom-free
	250	Discontinued	Menses remained relatively free of edema, headache and no visual blurring recurred.
6/9/41	250 discontinued. Stilbestrol, ½ mg. per day begun		
9/18/41	A.P.L. used for 10 days in July. None since. No potassium nitrate. Stilbestrol orally, ½ mg. 5 days preceding and succeeding menses.		Symptoms minimal. Fundi oculi normal. By this date the patient's weight had fallen gradually to 129 pounds.

TREATMENT AND SUBSEQUENT COURSE

Desiccated thyroid, 2 grains per day, and a low sodium diet and fluids limited to approximately 1200 cc. per day have been continued throughout. A placental extract containing estriol glucuronide (Emmenin) was used orally in doses of 1 dram four times daily for two months following September 26, 1940, and no improvement could be seen to follow it.

On September 30, 1941 the patient was seen again. She had continued the use of stilbestrol as outlined above but had followed no other therapy. Within the past month headaches have increased, and visible edema recurred with the last menstrual period. Her optic discs showed no evidence of pressure and her urea clearance test showed 90 and 83 per cent clearance in each of two hours, the blood urea being 33 mg. per cent.

COMMENT

The mechanism involved in the production of menstrual edema is not clearly understood. Recent studies in hormonal metabolism do afford some insight, however, into the process. The many points of interest cannot be discussed here, but a few of the salient ones may be recalled. The chief consideration is the fact that many of the steroid hormones have the power to cause retention of sodium, chloride, other electrolytes and water in the body. The adrenal cortical hormone desoxycorticosterone has a very powerful effect in this regard and no physician who has watched critically the effect of this hormone on the fall in hematocrit level and the rise in body weight of patients with Addison's disease could fail to be impressed. So great is this power that this hormone, if used in excessive amounts, may cause pulmonary edema and death. Thorn[15] has shown that the same type of action exists for estrone, estradiol, testosterone and progesterone. Such effects for testosterone propionate have also been shown by Kenyon[16], and for testosterone propionate and methyl testosterone by me [17, 18]. The fact that this power is not relegated to the estrogens alone, but to testosterone and progesterone as well, is interesting to consider here in view of the fact that both of these substances have been recommended for the therapy of phenomena similar to menstrual edema. Thorn[19] feels that the hormones of the adrenals and gonads may, under certain conditions, "act as precipitating factors in the production of edema". Whether a change in rate of excretion of these substances is a factor of importance is not certain. Such a mechanism has been suggested by Frank[20]. Further discussion as to the mode of action of pregnancy urine extract in cases of this kind would at present be more philosophical than scientific.

Various forms of treatment have been suggested. In Thomas'[4] case, calcium lactate and calcium gluconate were helpful and pregnancy urine extract produced spectacular improvement. In the case of Atkinson and Ivy[5], desiccated thyroid, ammonium nitrate, potassium chloride, calcium gluconate and viosterol failed. Good results were obtained at first with pregnancy urine extract, but these could not be repeated. Finally, a good result was obtained with an estrogenic placental extract (Emmenin) which contains estriol glucuronide. Thorn[19] recommends absolute restriction of sodium chloride in the diet for seven to ten days preceding the onset of menstruation, plus 10 cc. of a 20 per cent solution of potassium citrate in fruit juice two or three times daily.

Frank[20] reported good results in overcoming premenstrual tension with the use of magnesium sulfate by mouth, and recommended roentgen ray castration. In one case of severe premenstrual tension with neurologic signs, we prescribed roentgen therapy to the ovaries, with good results.

Hormones have been used for their antagonistic effect on estrogens and good results have been reported by Israel[21] following the premenstrual administration of progesterone, and Greenblatt[22] has used testosterone propionate successfully for the same purpose. Whether these later affect premenstrual molimina by virtue of hormonal action not dependent upon electrolyte response is not clear.

More recently Greenhill and Freed [23] ascribed premenstrual distress to retention of water in the tissues, and report excellent results following the qualitative restriction of sodium chloride, plus the oral administration of 1.0 gm. of ammonium chloride three times per day. In some of our cases apparently similar to the one reported above, subtemporal decompression has been necessary to prevent blindness.

Much more experience is needed in the management of menstrual edema before an accurate evaluation of the various types of therapy can be made.

SUMMARY AND CONCLUSIONS

Observations are reported on a case of menstrual edema with increased intracranial pressure (pseudotumor cerebri).

Hypothyroidism was a complicating feature, but the use of desiccated thyroid failed to control the recurrent edema.

Potassium citrate, sodium chloride, potassium chloride, and Emmenin appeared to influence the course of the disease little, if at all. Potassium nitrate in doses of 8 grams daily may have been of some value.

A. P. L. (Ayerst), a pregnancy urine extract, in large doses appears to have had a distinct influence upon the disease.

To the time of writing, the patient remains almost completely symptom-free, but there are evidences of mild exacerbations.

REFERENCES

1. Eufinger, H. and Spiegler, R.: Der Einfluss des mensuellen Zyklus auf den Wasserstoffwechsel, Arch f. Gynäk, 135:223-231, 1928.
2. Okey, R. and Stewart, D.: Diet and blood cholesterol in normal women. J. Biol. Chem. 99:717-727, (February) 1933.
3. Sweeney, J. S.: Menstrual edema; preliminary report, J.A.M.A. 113:234-236, (July 28) 1934.
4. Thomas, W. A.: Generalized edema occurring only at the menstrual period., J.A.M.A. 101:1126-1127, (October 7) 1933.

5. Atkinson, A. J. and Ivy, A. C.: Menstrual edema; report of case controlled by emmenin but not by theelol or theelin, J.A.M.A. 106:515-517, (February 15) 1936.

6. Quincke, H.: Ueber Meningitis serosa und verwandte Zustände, Deutsch. Ztschr. f. Nervenh. 9:149-168, 1897.

7. Davidoff, L. M. and Dyke, C. G.: A presentation of a series of cases of serous meningitis, J. Nerv. & Ment. Dis. 83:700-705, (February) 1936.

8. Warrington, W. B.: Intracranial serous effusions of inflammatory origin, Quart. J. Med. 7:93-117, (January) 1914.

9. Symonds, C. P.: Otitic hydrocephalus, Brain, 54:55-71, (April) 1931.

10. McAlpine, D.: Toxic hydrocephalus, Brain, 60:180-203, (June) 1937.

11. Sahs, A. L. and Hyndman, O. R.: Intracranial hypertension of unknown cause, Arch. Surg., 38:428-442, (March) 1939.

12. Gardner, W. J.: Otitic sinus thrombosis causing intracranial hypertension, Arch. Otolaryng. 30:253-268, (August) 1939.

13. Gustavson, R. G., and D'Amour, F. E.: A biologic assay of "international standard" estrin and of certain commercial preparations, J. Pharmacol. and Exper. Therap. 57: 472-481, (August) 1936.

14. McCullagh, D. R. and McLin, T. R.: Extraction of androgens from urine, Endocrinol. 22:120-121, (January) 1938.

15. Thorn, G. W. and Engel, L. L.: Effect of sex hormones on renal excretion of electrolytes, J. Exper. Med. 68:299-312, (September) 1938.

16. Kenyon, A. T., Knowlton, K., Sandiford, I., Koch, F. C. and Lotwin, G.: A comparative study of the metabolic effects of testosterone propionate in normal men and women and in eunuchoidism, Endocrinol. 26:26-45, (January) 1940.

17. McCullagh, E. P. and McGurl, F. J.: Effects of testosterone propionate on epiphyseal closure, Na and Cl balance and on sperm counts, Endocrinol. 26:377-384, (March) 1940.

18. McCullagh, E. P. and Rossmiller, H. R.: Methyl testosterone. II. Calorigenic activity, J. Clin. Endocrinol. 1:503-506, (January) 1941; III. Effect upon body weight and growth, J. Clin. Endocrinol. 1:507-510, (June) 1941.

19. Thorn, G. W. and Emmerson, K.: The role of gonadal and adrenal cortical hormones in the production of edema, Ann. Int. Med. 14:757-769, (November) 1940.

20. Frank, R. T.: Hormonal causes of premenstrual tension, Arch. Neurol. & Psychiat. 26:1053-1057, (November) 1931.

21. Israel, S. L.: Premenstrual tension, J.A.M.A. 110:1721-1723, (May 21) 1938.

22. Greenblatt, R. B.: Syndrome of Major menstrual molimina with hypermenorrhea alleviated by testosterone propionate, 115:120-121, (July 13) 1940.

23. Greenhill, J. P. and Freed, S. C.: Electrolyte therapy of premenstrual distress, J.A.M.A. 117:504-506, (August 16) 1941.

RECOVERY FROM OTITIC PNEUMOCOCCIC MENINGITIS

Report of Two Cases

PAUL M. MOORE, Jr., M.D.

No attempt will be made in this report to review the extensive literature on pneumococcic meningitis. Suffice it to say that prior to the advent of chemotherapy there were no recoveries from this condition, in spite of desperate attemp's to control the disease by early and complete operations on the mastoid, with extensive exposure of the dura and repeated or continuous drainage of the spinal fluid. Since the use of the sulfonamide drugs, especially in conjunction with the type-specific antipneumococcic serum, numerous recoveries have been reported.

CASE REPORTS

The first of these two cases was a typical Type III pneumococcic infection in the ear, with subsequent meningitis. The second case was a Type I pneumococcic meningitis which developed suddenly from an otitis media without mastoid involvement. Chemotherapy and the type-specific antipneumococcic serum were used in both cases. In the first case the mastoid was operated upon late in the treatment to prevent a recurrence. In the second case, surgery was unnecessary. Both patients recovered completely and have had no further complications.

Case 1: A white man, 62 years of age, was admitted to the hospital in August, 1938, in a semistuporous condition. Three months previously, in May, he had had an acute infection of the upper respiratory tract, with a temperature of 100 to 101° F., headache, and a right otalgia. A week after the onset there was a discharge from the right ear for about twenty-four hours. He gradually felt better and was able to do some work, but he continued to have a temperature of 100° F, and a headache. He felt much better during the following month. However, about the middle of July, the headaches became more severe. He had some right otalgia at all times during this period. Thirty-six hours before admission to the hospital he went to bed with increased otalgia, headache, and general malaise. He became very drowsy. On the morning of admission to the hospital he vomitted several times, and it was noted that his neck was rigid.

Examination revealed a well-developed, elderly man in a semistuporous condition. The skin and mucous membranes were dry and the tongue was coated. The pupils, which were very small as the result of a previous administration of morphine, were regular and equal, and reacted sluggishly. The extra-ocular movements were normal and there was no nystagmus. The left ear was normal. The right external auditory canal and drum were discolored from the previous use of some type of ear drops. There was no pus in the right canal. The right ear drum was intact, but was thickened and had lost its lustre. It had a dirty grey appearance and showed some fulness. There was no injection. No edema nor tenderness was present over the right mastoid. The chest was of the emphysematous type. The heart, lungs and abdomen were normal. All of the cranial nerves were intact. The biceps reflexes were active and the patellar reflexes were very sluggish, the left being more active than the right. There was a two-plus Brudzinski's sign, a one-plus Kernig's sign, and a plus-minus Babinski reflex on the left.

The temperature was 101.8° F. Soon after admission, however, it rose to 103.2° F. Roentgenograms showed both mastoids to be of the small celled type. The left mastoid was normal. The right mastoid was quite cloudy, but showed no evidence of destruction of bone. (Fig. 1.) Both petrous tips were without cellular content. The paranasal sinuses were normal. Lumbar puncture obtained cloudy spinal fluid under a pressure of 250 mm. of water. The pressure rose to 300 mm. on deep jugular compression, and fell to 120 mm. after the withdrawal of 10 cc. of spinal fluid. The fluid contained 1,420 cells, most of which were polymorphonuclear leukocytes. Culture of the spinal fluid yielded a Type III pneumococcus. Sulfanilamide and sodium bicarbonate were given by mouth, and 20,000 units of Type III antipneumococcic rabbit serum were administered intravenously after carefully testing for sensitivity with skin and conjunctival tests, and by injecting small quantities subcutaneously. A myringotomy was done on the right drum and a small amount of thick, tenaceous mucopus was obtained. Blood cultures were negative, as were Wassermann and Kahn tests of the blood.

On the fourth day after admission, the temperature was normal and he was mentally alert. The spinal fluid contained 160 polymorphonuclear leukocytes, and culture of the fluid was negative. On the seventh day the headache and rigidity of the neck disappeared. From the fourth to the eleventh day the patient had to be catheterized because of bladder retention. On the twelfth day, the spinal fluid contained only 8 cells and the pressure was normal.

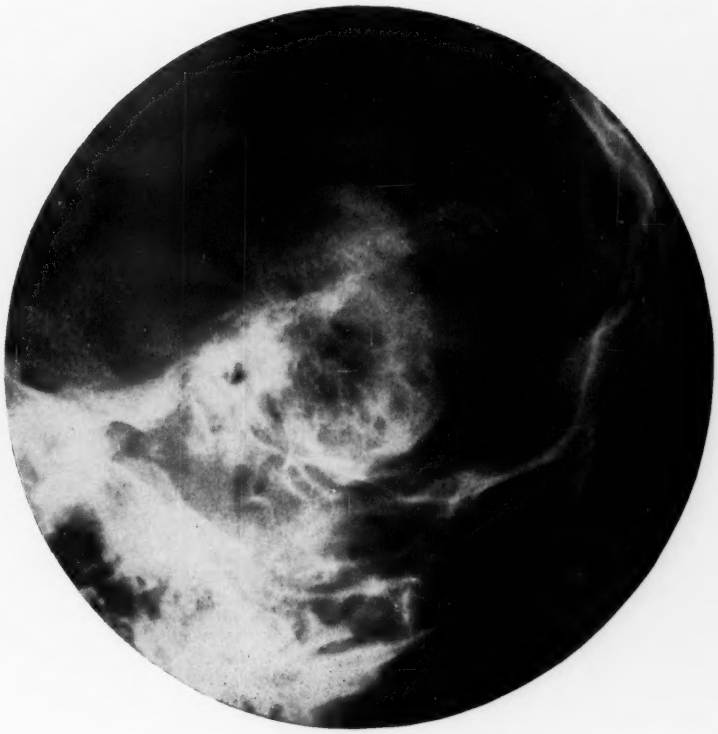


FIGURE 1 (Case 1): Roentgenogram of right mastoid.

The right ear drained for only a few days after the myringotomy, and at no time was there any edema or tenderness over the mastoid. Audiograms showed normal hearing on the left side, and the right curve was about 10 db below the left. Bone conduction was prolonged. The Weber test was referred to the right ear. Rinne's test was negative on the right and positive on the left. Progress roentgenograms of the mastoid showed continued cloudiness of the cells, and it was felt unwise to discharge the patient without clearing up the primary focus of the meningitis. Accordingly, on the twenty-second day in the hospital, a simple mastoid operation was done on the right side. He was discharged fourteen days later. No destruction of bone was found at the time of operation, but the antrum contained thick mucopus, and the cells were completely filled with thickened membrane. Cultures taken from the mastoid were negative.

Determinations of the sulfanilamide concentration in the blood showed 14.7 mg. per 100 cc. on the second day, 13.1 mg. on the fourth, 9.2 mg. on the sixth, 8.5 mg. on the eighth, 7.7 mg. on the tenth and eleventh, and 5.0 on the twelfth day, at which time the drug was discontinued. Determinations of the red and white cells of the blood and hemoglobin content were made every other day. The red cell count remained at 4,250,000 or more, and the white cell count ranged from 13,350 to 6,000. The hemoglobin was 65 per cent the first day, and ranged from there to 84 per cent.

Equal amounts of sulfanilamide and sodium bicarbonate were given throughout the period of medication. On the first day 30 grains each were given on admittance and at 2:00 p.m., 60 grains at 6:00 p.m., 30 grains at 10:00 p.m., and 15 grains at 12 midnight. Following the ten o'clock dosage the patient had an emesis of 90 cc. Therefore, he did not retain all of the 135 grains given the first day. On the second day 15 grains were given every two hours until 2:00 p.m., and then 20 grains at 8:00 p.m., totaling 125 grains. On the third, fourth and fifth days he received 20 grains every six hours, totaling 80 grains a day. On the sixth day 55 grains were given, and 30 grains were given in divided doses on each of the seventh and eighth days. On the ninth, tenth and eleventh days, 15 grains a day were administered. The total amount of sulfanilamide received during the eleven days was 660 grains, of which less than 30 grains were lost by emesis.

This case was treated before the routine of a large initial dose followed by regular smaller doses every four hours had been established.

Comment: This case was the first in our experience to recover from an otitic pneumococcic meningitis. The infection was typical of Type III pneumococcus. The original infection in the ear occurred three months prior to the onset of the meningitis. It was felt that his only salvation lay in the use of chemotherapy, and as soon as the infecting organism was definitely identified, the type-specific rabbit serum was administered. The operation on the mastoid was delayed because it was felt that it would be futile unless the chemotherapy was effective. He responded so well to the use of chemotherapy that operation was withheld until complete recovery from the meningitis occurred, and then it was done only to prevent a possible recurrence.

Case 2: A 13 year old white girl was admitted to the hospital in February, 1941, in coma. Eleven days before admission, during the course of a cold in the head, an acute otitis media developed on the left side. This ruptured spontaneously, and the drainage seemed adequate to the attending physician. Five days before admission to the hospital 15 grains of sulfanilamide was given, followed by 5 grains every four hours. This was discontinued after two days, however, because of nausea. The temperature remained normal and except for the otorrhea, she was quite well until 5 p.m. of the day preceding admission, when a left facial paralysis occurred, with headache and pain in the neck, accompanied by a sudden rise in the temperature. At 8:00 p.m. the neck was rigid and she gradually became less responsive.

Examination revealed a gravely ill girl in coma. The neck was rigid, partially extended, and held to the left. There was a conjugate deviation of the eyes to the left, associated with a spontaneous horizontal nystagmus to the left. A peripheral type of facial paralysis was present on the left. The reflexes were hypoactive and Babinski's reflex was absent. She cried out when moved. The left external auditory canal contained a bloody, purulent discharge. The left drum was dull, injected, and bulging. There was no tenderness or edema over the left mastoid and roentgenograms showed a normal petrous tip and normal mastoid cells. The right ear drum and canal were normal. The nasal passages were clean and clear. The tongue was moist and the pharynx was moderately injected. The anterior cervical glands were palpable bilaterally. The chest showed equal expansion and the lungs were clear to percussion and auscultation. The heart was not enlarged, the rhythm was regular, and there were no murmurs. Except for bladder dullness from the symphysis to the umbilicus, abdominal examination was negative. The temperature was 102.6° F., the pulse rate 100, the respirations 25, and the blood pressure 110 mm. systolic, 70 mm. diastolic. On lumbar puncture the spinal fluid pressure was 200 mm. of water. It rose to 350 mm. on left jugular compression, to 340 mm. on right jugular compression, and to 550 mm. on bilateral compression. The pressure fell to 115 mm. after the removal of 10 cc. of cloudy, ground-glass appearing spinal fluid. The fluid contained 4,000 white blood cells, with 90 per cent polymorphonuclear leukocytes, a trace of globulin, and 320 mg. of protein. Cultures of the spinal fluid and of pus from the left ear produced Type I pneumococci. A culture of the blood was sterile.

A left myringotomy was done on the first day (February 6) and 3 grams of sulfapyridine were given intravenously, followed by 1500 cc. of 5 per cent glucose solution. On the following morning the report of the culture was received, and 100,000 units of Type I antipneumococcic rabit serum was administered intravenously after first testing for sensitivity. Fluids were given through a nasal feeding tube. From the second to the sixth days she received an initial dose of 2 grams of sulfapyridine, and 1 gram every

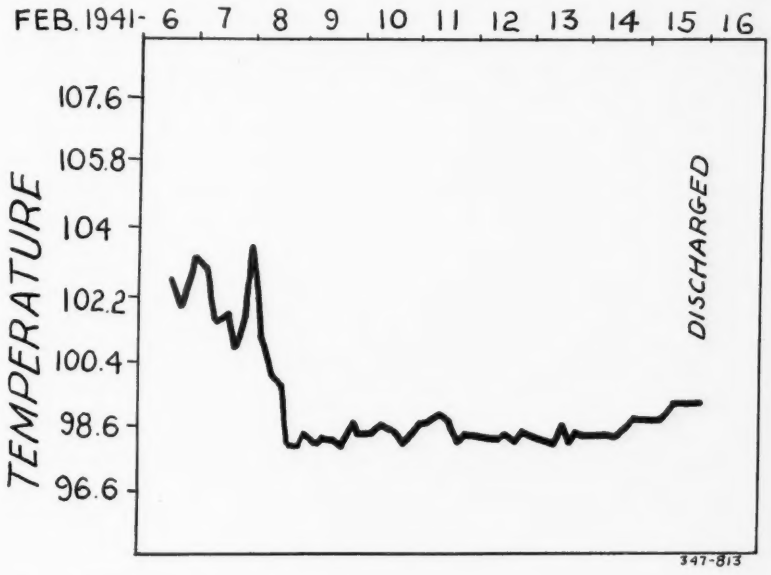


FIGURE 2 (Case 2): Temperature chart.

four hours through the tube. She was given 3.5 grams of sulfapyridine intravenously on the third day, followed by a transfusion of 500 cc. of blood. On this day the temperature became normal (Fig. 2), and remained normal during the rest of the period of hospitalization. The conjugate deviation of the eyes disappeared and the movements of the eyes were free. The rigidity of the neck became less and her cry was more normal. At times she showed some response to questioning. Four days after admission to the hospital she was fully conscious and there was practically no rigidity of the neck nor facial paralysis. She would not permit removal of the nasal feeding tube because she thought that she would be unable to swallow. She agreed to its removal on the following day, however, (February 11). At this time the ear was dry and she was free from symptoms. Seven days after admission the spinal fluid showed 200 white blood cells, which were chiefly lymphocytes, and 95 mg. protein. Smears and cultures were negative for organisms. She was given a soft diet on this day. Roentgenograms of the mastoid on the ninth day were normal. She was allowed out of bed the following day and was discharged from the hospital on February 16, ten days after admission to the hospital.

Determinations of the blood sulfapyridine concentration showed 1.2 mg. per 100 cc. the second day, 3.0 on the third day, 2.7 the fifth, and 2.5 mg. the sixth day. On February 7 the red blood cells numbered 3,790,000; the white blood cells, 12,900; and the hemoglobin was 61 per cent. Five days later the red blood cells numbered 5,000,000; the white blood cells, 6,050; and the hemoglobin was 84 per cent. Wassermann and Kahn tests of the blood were negative. The total dosage of sulfapyridine was 486 grains by mouth and intravenously.

Comment: This case represents a truly miraculous recovery accomplished by the use of serum and chemotherapy. When admitted to the hospital the patient was in a deep coma, with full-blown meningitis and organisms in the spinal fluid. The conjugate deviation of the eyes suggested involvement of the brain stem and was a grave prognostic sign. The infection had bypassed the mastoid and had entered directly into the meninges from the tympanum. The facial nerve probably was involved in the tympanum itself. In spite of this desperate picture, she responded to treatment and was discharged from the hospital ten days after admission, completely recovered from the meningitis, facial paralysis, and the infection in the ear. Before the patient was discharged, a second roentgenogram was taken of the mastoid to make sure that no involvement had occurred which might act as a focus for future complications.

A myringotomy was the only surgical procedure. Before the advent of the sulfonamide drugs and the type-specific antipneumococcic serum, the accepted method of treatment was an immediate operation on the mastoid, regardless of negative roentgenograms. Had this procedure been followed, in all probability this girl would not have recovered.

DISCUSSION

Two cases obviously form an inadequate basis on which to draw conclusions. It would seem, however, that early identification of the infecting organism, followed immediately by the use of the type-specific serum and the appropriate sulfonamide preparation given to near the limit of tolerance, form a rational basis of treatment. Immediate mastoid surgery, therefore, would no longer seem necessary.

THE PNEUMOCOCCUS IN INFECTIONS OTHER THAN PNEUMONIA

Importance of Increased Recognition Because of the Efficacy of Chemotherapy

H. S. VanORDSTRAND, M.D.

Many of us think of and search for the pneumococcus in pneumonic disease only, even though it has been known for many years that this specific organism can cause or complicate infection in parts of the body other than the lungs. Since Fränkel recognized the pneumococcus in 1886, this organism usually has been considered as the cause of severe disease processes. When thinking of the pneumococcus in apneumonic conditions, most of us associate it with such serious diseases as peritonitis and meningitis. On the contrary, in recent years it has been shown that many people are carriers of this organism, which is harbored as part of the bacterial flora, particularly in the upper respiratory tract and at certain seasons of the year, with no pathogenic effects. The advent of chemotherapy has renewed interest in the search for the pneumococcus in all its habitats. In pneumococcic infections other than pneumonia, chemotherapy has been of equal value in reducing mortality. As these infections are ordinarily more benign than pneumonia, however, the reduction in morbidity has been of even greater importance.

At the Cleveland Clinic in the past twenty-four months, one or more types of pneumococci have been bacteriologically demonstrated from 51 patients who were suffering from diseases other than pneumonia. The variety of sources of pneumococci and of conditions from which these patients were suffering, as well as their response to chemotherapy, when employed, has been enlightening. It is the purpose of this presentation to review the varying habitats and pathogenicity of the pneumococcus as seen in this group of patients, as well as to illustrate the importance of chemotherapy in reducing morbidity.

The most common form of the pneumococcus is the so-called lance-shape, which usually occurs in pairs (diplococci), each pair being surrounded by a single capsule. However, it is often difficult to recognize, as it may be found in chains of single cocci which are not lance-shaped, especially in an avirulent form. The capsule may likewise be absent or non-demonstrable at times. Fortunately, it stains readily with all the usual aqueous aniline dyes. As everyone is constantly on the lookout for this organism, it may be suspected even in abnormal forms, and its presence proved through Neufeld's staining and typing. When secretions to be examined are very scant, they may first be implanted on Löffler's medium which, in the presence of pneumococci, will allow rapid growth

and secondary typing within a few hours. The pneumococcus, although difficult to grow on some media, is both aerobic and anaerobic. Neufeld, in 1910, first recognized the presence of varying types; newer ones were recognized in succeeding years, the last being Type XXXIII. Only Type III can be classified on smear alone, chiefly because of its large capsule. It has long been known as Streptococcus mucosus.

The source of material in 51 patients suffering from diseases other than pneumonia was as follows:

Sputum	18
Ear	9
Bronchoscopic aspiration	7
Throat	5
Paranasal sinus	4
Pleural fluid	3
Peritoneum	1
Joint	1
Culture of post-thyroidectomy wound infection	1
Culture of primary brain abscess	1
Culture of extradural abscess of spinal cord	1
Total	51

All of these patients had one or more examinations of the chest, including roentgenograms. In no patient was pneumonia demonstrable.

The following seasonal relationship was noted:

January	3
February	4
March	6
April	5
May	6
June	6
July	0
August	1
September	3
October	3
November	7
December	7
Total	51

This agrees in some measure with the seasonal incidence of the pneumococcus and pneumococcic pneumonia as found in public health surveys.

The pneumococci were type-specific as follows (58 type-specific pneumococci were found in 51 patients; 2 patients had 3 types each, and one had 4).

Type I	2	Type XVII	2
Type II	1	Type XVIII	2
Type III	19	Type XIX	1
Type IV	1	Type XX	2
Type V	0	Type XXI	2
Type VI	1	Type XXII	4
Type VII	4	Type XXIII	0
Type VIII	5	Type XXIV	2
Type IX	0	Type XXV	0
Type X	0	Type XXVI	0
Type XI	2	Type XXVII	0
Type XII	0	Type XXVIII	0
Type XIII	2	Type XXIX	1
Type XIV	1	Type XXX	0
Type XV	1	Type XXXI	1
Type XVI	0	Type XXXII	0
		Type XXXIII	3

The Type III pneumococcus was found to be the most frequent, the other types being fairly well distributed.

The clinical diagnosis in this group of 51 patients varied as follows:

Acute infection of upper respiratory tract (common cold)	9
Otitis media	9
Acute 7	
Chronic 2	
Bronchiectasis	7
Chronic bronchitis, for which no cause except the pneumococcus could be found	5
Chronic suppurative sinusitis, paranasal	4
Incidental (cases of benign tumor of the mouth, rheumatic heart disease, and lung tumor)	3
Empyema (2 postoperative to pneumonectomy for primary carcinoma, and 1 associated with chronic lung abscess)	3
Asthma	3
Asthmatic bronchitis	2
Septic arthritis	1
Pulmonary aspergillosis	1
Peritonitis, secondary to perforated peptic ulcer	1
Primary brain abscess	1
Extradural abscess of the spinal cord	1
Post-thyroidectomy wound infection	1

TREATMENT

The diagnostic groups of patients are further discussed, particularly with reference to results of chemotherapy.

The 9 patients with acute infections of the upper respiratory tract described their colds as persistent, and of at least several weeks' duration, for which reason sputum or nasal or throat swab specimens were examined. Since the pneumococcus was present, all these patients were given chemotherapy, sulfapyridine being used in 3 cases and sulfathiazole in 6, with quite prompt subsidence of symptoms.

None of the 7 patients with acute otitis media was treated with chemotherapy. In each case the pneumococcus was found on establishment of drainage, the latter being the curative procedure. Sulfathiazole powder was used in one case of chronic otitis media, and was felt to be very helpful.

Chemotherapy was found to be particularly helpful in the 7 cases of bronchiectasis. In addition to a long-standing, copious, productive cough, 4 of the patients had had recurrent bouts of fever every two to six weeks. The attacks of fever promptly subsided following a course of sulfathiazole therapy and have not recurred to date. All 7 patients were found to have advanced bronchiectasis shown by lipiodol bronchograms, and were treated medically, 4 having lesions contraindicating surgery and the other 3 refusing surgical intervention. In 3 cases chemotherapy reverted the lesion to a dry stage with no other treatment. In summary, chemotherapy was of much symptomatic benefit in all the cases of bronchiectasis. One of the cases is reported as follows:

A 55 year old steel worker was seen at the clinic in November, 1940 because of a chronic, productive cough with recurrent bouts of fever of one-half to one year's duration. He stated that his symptoms followed lobar pneumonia. He expectorated from 6 to 8 ounces of purulent sputum daily, which was foul when associated with fever. Every two to four weeks the temperature was elevated 1 or 2 degrees for periods of two or three days.

Roentgen examination of the chest showed entirely normal findings except for an increase of the bronchial markings in the right base. Lipiodol bronchograms revealed a saccular type of bronchiectasis of the right lower lobe.

Bacteriologic study of purulent secretion aspirated through the bronchoscope showed the principal organism to be Type XXI pneumococcus. The other laboratory studies showed nothing of significance except for an elevation of the white blood cell count to 14,100.

The patient was advised to have a lobectomy, but this was refused. Sulfapyridine in doses of 4 grams daily was used, and he was instructed in postural drainage exercises. He did not carry out the latter, but when seen one week later, stated that his cough had entirely disappeared. He subsequently has followed no treatment of any kind, but has reported at intervals. When last seen on August 13, 1941, he had had no recurrence of cough and there had been complete freedom from the bouts of fever.

The 5 patients with chronic bronchitis had a chronic, slightly productive cough varying from 6 to 12 weeks in duration. Bronchoscopic examination performed in 3 cases revealed no abnormalities other than slight hyperemia of the tracheobronchial mucosa. The examination revealed no other possible cause for the symptoms, and chemotherapy promptly cured them in 4 of the 5 cases.

In the 2 cases of pneumococcic empyema complicating pneumonectomy for primary carcinoma, intensive chemotherapy was given orally and intravenously. Recovery occurred without the necessity of rib resection and drainage. In both cases the surgical incision was closed without tube drainage at the time of the operation. The patient with the chronic lung abscess of eight months' duration with empyema was

treated by incision and drainage along with chemotherapy one year ago. When seen on September 21, 1941, she was completely well, the lung being roentgenographically normal and the surgical drainage site entirely healed.

Of the 3 patients manifesting asthma, one was treated with combined allergy management and chemotherapy, and the other 2 with chemotherapy alone, with satisfying results. One of the latter cases is summarized as follows:

A 40 year old grocer was admitted to the hospital on January 28, 1940, complaining chiefly of periodic attacks of asthma over the previous 20-year period. According to the referring physician, he had been in status asthmaticus during the previous three weeks.

The general physical examination was negative except for the typical findings of asthma. Sibilant and sonorous inspiratory and prolonged expiratory rhonchi were heard in all lung fields. No moist râles were elicited.

Roentgen examination of the chest showed a bilateral minimal apical lesion of tuberculous type. Activity could not be determined from the roentgenographic appearance. The remainder of the lung fields was entirely clear. In addition, lipiodol bronchograms were made for complete exclusion of bronchiectasis.

Bronchial secretion obtained through the bronchoscope revealed that the predominant organism was Type III pneumococcus.

The patient was placed on sulfanilamide therapy. He left the hospital after only five days' stay. The examining physician maintained the sulfanilamide therapy in dosages of 90 grains daily for the succeeding three weeks at home. The patient was entirely freed of his asthma in two weeks, and when last heard from six months ago, had remained symptom-free. Progress roentgenograms at intervals of six months have shown the apical lesion to be stationary. The diagnosis of arrested minimal tuberculosis has no bearing on the asthma.

In the 2 patients clinically suffering from asthmatic bronchitis, the demonstration of the type-specific pneumococcus was particularly helpful. It was felt to be the cause of the symptoms, and was proved to be such by the response to chemotherapy. A case history of one of these patients follows.

A 62 year old grocer was seen at the clinic on April 11, 1941, for recurrent attacks of asthmatic bronchitis. He stated that he had always been in the best of health until a little over two years previously, at which time he developed a head cold which then progressed into bronchitis. He described the latter as paroxysmal coughing with white, thick, mucoid expectoration, shortness of breath, and wheezing. The shortness of breath and wheezing were entirely related to the paroxysms of coughing, would occur at any time day or night, and were not described as true bronchial asthma. An attack observed at the clinic was not thought to be bronchial asthma. According to the history, the initial episode lasted for six or seven weeks. Since then the patient had had a recurrence every three or four months with each episode slightly longer, so that he was having only three or four week intervals of freedom. In these intervals he was entirely free of all symptoms. The patient stated that his present period of asthmatic bronchitis had lasted one week.

The positive findings on the physical examination were entirely limited to the chest. They consisted of a moderate degree of emphysema, an increase in the anteroposterior chest diameter, with a hyperresonant percussion note in the lower half of both lung fields, with diffusely scattered fine, sibilant inspiratory rhonchi throughout both lungs. The temperature was normal.

Roentgen examination of the chest revealed diffuse, fine, nodular fibrosis of the silicotic type with no evidence of an exudative lesion.

The bronchoscopic examination showed the trachea in the midline, and the carina normal in shape and position, with the bifurcation angle normal. The entire tracheobronchial mucous membrane, however, was deeply injected with several patchy areas of granulation, the latter most prominent in the main stem bronchi. A considerable amount of mucopurulent secretions was aspirated from both main stem and bronchi, and the study of these secretions revealed the predominant organism to be diplococci. The Type III pneumococcus was recognized on smear alone, and typing not only confirmed this but revealed Types XIII, XVII, and XXII as well. The aspirated secretions were negative for tubercle bacilli, fusospirochetes and fungi on complete smear and culture studies. The patient was placed on a course of sulfathiazole therapy, 6 grams of the drug daily for four days and then 4 grams daily for the succeeding ten days. Within one week's time he was entirely symptom-free, and when seen again for recheck examination four months later had remained so. A recheck roentgen examination of the chest at the last visit showed no change in the fine, diffuse nodular fibrosis and no evidence of any exudative lesion.

The patient was particularly interesting because his pneumococcic asthmatic bronchitis complicated an asymptomatic minimal silicosis. The patient had been a coal miner from the age of 25 to 45 years, with no history of silica exposure in the seventeen year interval before he was seen at the clinic. His case was further of particular interest because of the bronchoscopic demonstration of tracheobronchial lesions from which the pneumococci were obtained.

In the case of septic arthritis, a type-specific pneumococcus was aspirated from one of the three joints involved, and the symptoms and objective findings entirely disappeared after one week of drug therapy.

No follow-up has been obtained on the one patient in whom a pneumococcus was felt to be complicating pulmonary aspergillosis (Aspergillis niger).

Chemotherapy was used for only one of the patients suffering from chronic suppurative sinusitis, all 4 patients having fundamentally maxillary infections, and the result was gratifying. The other 3 patients having pneumococcic suppurative maxillary sinusitis were treated only by saline irrigation of the involved antra via the natural ostia (the maximum number of irrigations being four), with apparent equal improvement and subsidence of the infection.

The patient with pneumococcic peritonitis died before chemotherapy could be used. He presented a most unusual problem in that his fundamental trouble was a perforated peptic ulcer. When brought to the hospital he was critically ill, and a laparotomy was immediately performed because of the suspected ulcer perforation. In addition to the ulcer perforation, the laparotomy revealed diffuse peritonitis, all cultures of which revealed pure Type III pneumococci. The patient died three hours postoperatively, and autopsy showed no evidence of pneumonia.

In the case of primary brain abscess caused by a Type III pneumococcus, death followed the establishment of the etiologic diagnosis before chemotherapy could be instituted.

In the case of extradural abscess of the spinal cord, also due to Type III, the infection was eradicated through a combination of chemotherapy and surgical drainage. It is problematical which treatment was of most value, although chemotherapy was felt to be as helpful as drainage in preventing any further complication. However, when the patient left the hospital, it was felt that he would probably have permanent cord changes because of the longstanding cord compression prior to the establishment of treatment.

In the case of postoperative thyroidectomy wound infection of pneumococcic origin, Type III, irrigations of the wound with sulfanilamide solution quickly eradicated the complication. The wound infection appeared on the third postoperative day. The temperature returned to normal within twenty-four hours after the institution of chemotherapy, and the convalescence was steady and uneventful from that time.

SUMMARY

Because of the advent of chemotherapy, it was felt worth while to review a series of 51 cases seen at the clinic during the past twenty-four months in which the pneumococcus was associated with conditions other than pneumonia. Chemotherapy was used in the majority of these cases as effectively as it is used in pneumonia. As apneumonic infections on the whole normally have a much lower mortality, the chief importance of chemotherapy was found in the reduction of the morbidity of the infection. Observance of the response to trial chemotherapy in certain cases was of much help in evaluating the etiologic importance of the pneumococcus found.

The therapeutic test was used because of the well-known fact that the pneumococcus may be harbored in many people in asymptomatic forms. The therapeutic test seemed to indicate that the pneumococcus prolonged and enhanced the symptoms, as well as being an important etiologic factor in certain cases, particularly of severe acute upper respiratory infection, chronic bronchitis in which no other etiology could be found, certain cases of asthma and asthmatic bronchitis, certain cases of chronic suppurative sinusitis and bronchiectasis.

The series of 51 cases was reviewed with reference to source of material for bacteriologic study, seasonal incidence, variety of types of pneumococcus, clinical diagnosis and response to treatment.

TOTAL GASTRECTOMY

Report of a Case

T. E. JONES, M.D.

The following case is reported to point out several features. First, the tardiness with which these patients present themselves. This patient had gastric symptoms for a year before the diagnosis was made, a situation which has a distinct bearing upon operability and curability. Second, total gastrectomy is a feasible operation in selected cases, as many reports in the past ten years have indicated. This patient had sixteen months of comfortable productive life, whereas, I am sure, ten years ago total gastrectomy would have been considered impractical. Third, this case demonstrates that without any anti-anemic therapy the patient was able to maintain an active life and a stationary weight with a normal blood volume and cell counts.

CASE REPORT

A man, 44 years of age, was admitted to the hospital in April, 1940. He complained of a dull, gnawing epigastric discomfort of one year's duration, which occurred immediately after meals and was not relieved by food or antacids. There had never been any nausea or vomiting. The bowel habits were normal and no tarry stools had been noted. The patient had lost 20 pounds in weight since the onset of his illness, which he attributed to a gradual loss of appetite.

Physical examination revealed no abnormalities. The patient weighed 206 pounds, and appeared to be in good general health. No abdominal masses, organs, or clavicular nodes were palpable. Examination of the rectum was negative. The red blood cells numbered 4,900,000, and the hemoglobin was 91 per cent.

A roentgenogram of the stomach demonstrated a constant narrow channel in the pars media with some rigidity of the walls and an obliteration of the normal mucosal markings (Fig. 1). The stomach emptied rapidly, peristalsis passed normally through the distal third of the stomach, and the duodenal bulb filled well.

An exploratory operation was done on the upper abdomen. The middle third of the stomach was involved by an extensive infiltrating neoplasm which was confined chiefly to the posterior wall and the lesser curvature. The lesion was mobile. Several glands were thought to be palpable in the gastrohepatic omentum, but there was no gross evidence of glandular metastasis. The liver was normal and there was no evidence of metastasis to the rectovesical pouch. The entire stomach was resected. A loop of jejunum was brought through the transverse mesocolon and anastomosed to the esophagus with three rows of silk sutures. A Levine tube was passed into the proximal jejunal loop,

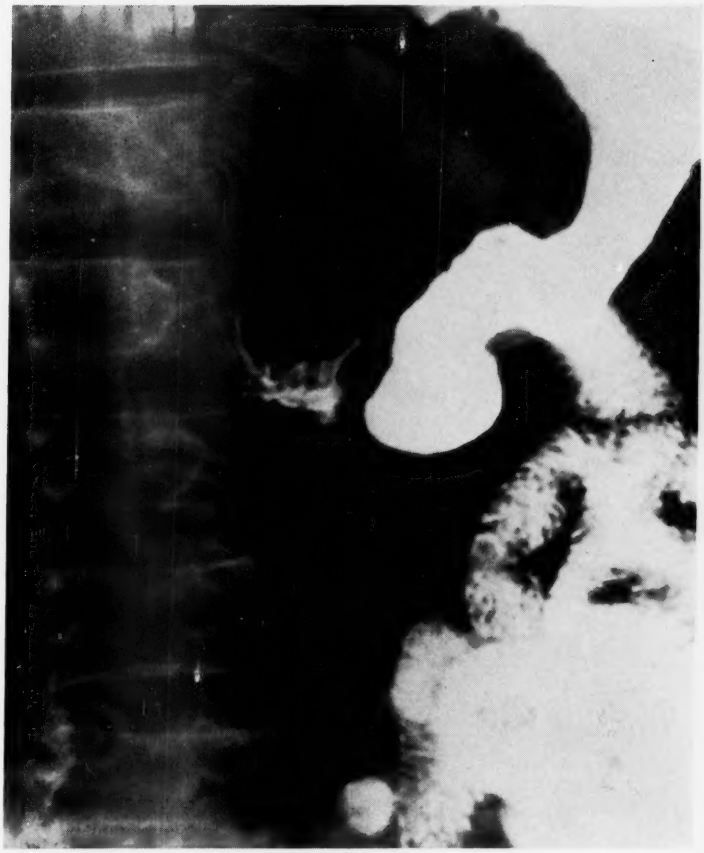


FIGURE 1: Roentgenogram of the stomach showing a constant narrow channel in the pars media with some rigidity of the walls and an obliteration of normal mucosal markings.

and an entero-enterostomy was made distal to the anastomosis and below the transverse mesocolon.

The postoperative course was uneventful, except for a mild lobar atelectasis. The patient was discharged from the hospital on the twenty-first postoperative day.

Pathologic examination of the stomach showed no evidence of involvement of the peritoneal surface and no ulceration of the mucosa. The rugae were hypertrophied and the entire stomach wall was thickened and nodular, particularly in the middle third. Microscopic examination showed a highly undifferentiated neoplasm with no tendency to form glands. There was no evidence of metastasis to regional lymph nodes removed with the stomach.

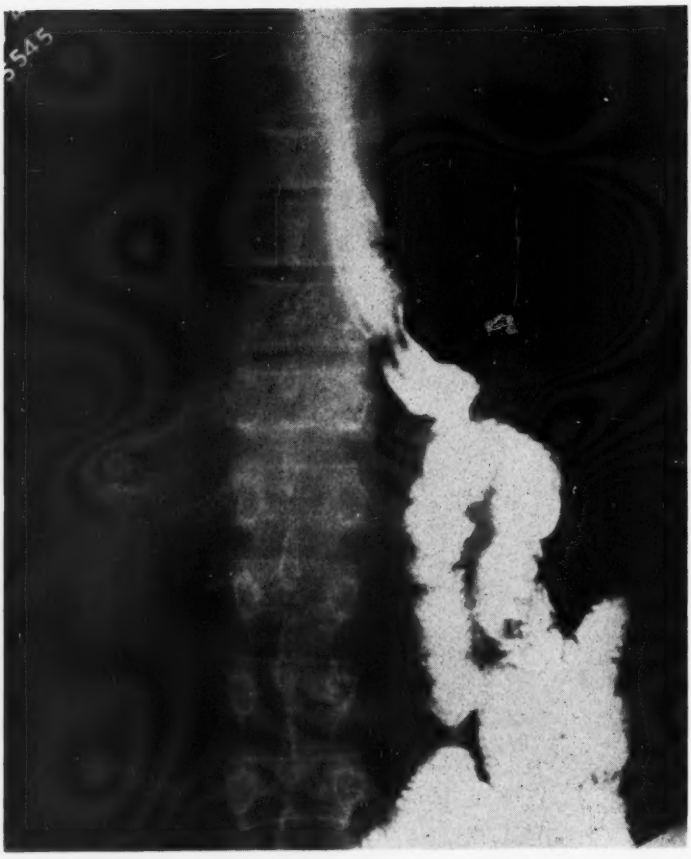


FIGURE 2: Roentgenogram after a barium meal, showing the stoma to be functioning well.

This patient was well for sixteen months and worked daily as an electrician until a few days before his second admission in September, 1941. He had had almost no difficulty with his diet, and within the first month postoperatively he was able to eat three full meals a day without restrictions. A constant weight of 170 pounds had been maintained. The red blood cell count, hemoglobin, and color and volume indices of the blood remained within normal limits without anti-anemic therapy.

In September, 1941, at our request, the patient returned for radiologic examination. His general health was good. A barium meal showed the stoma to be functioning well (Fig. 2). The day after this examination the patient complained of abdominal

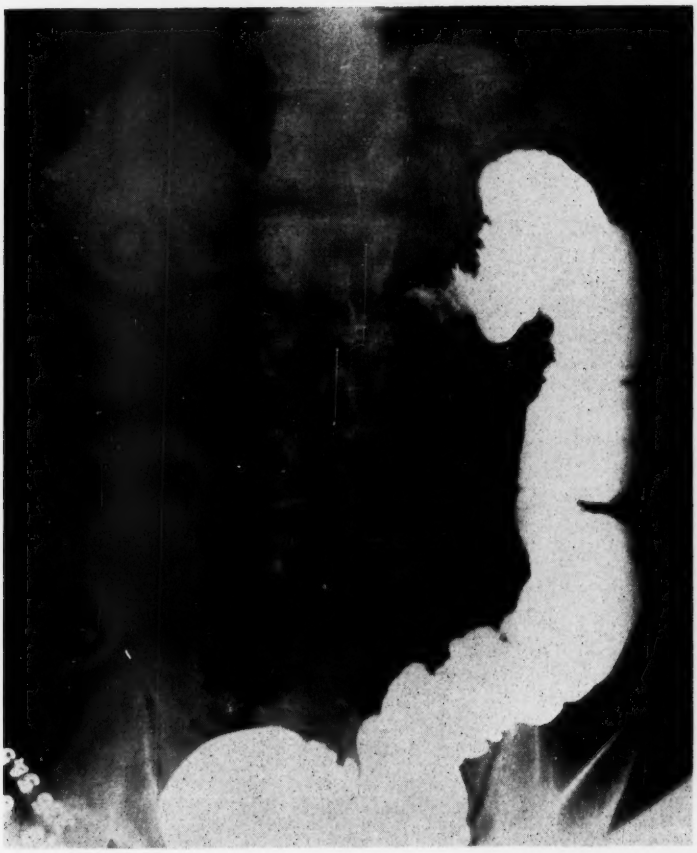


FIGURE 3: Roentgenogram of the abdomen 48 hours after barium meal, showing an annular, obstructing lesion just proximal to the splenic flexure of the colon.

cramps and some distention. A plain roentgenogram of the abdomen, forty-eight hours after the barium meal, showed an annular, obstructing lesion just proximal to the splenic flexure of the colon (Fig. 3). Following the use of enemas and small doses of Epsom salts the barium was expelled and the abdominal distention subsided. The patient stated, in retrospect, that he had noted an occasional abdominal cramp for one week before this admission, but that the bowel habits had not changed in any way.

The lesion near the splenic flexure was again visualized following a barium enema (Fig. 4). Mucosal markings were observed through the obstructed area. The radiologic diagnosis was colonic obstruction, extrinsic in origin.

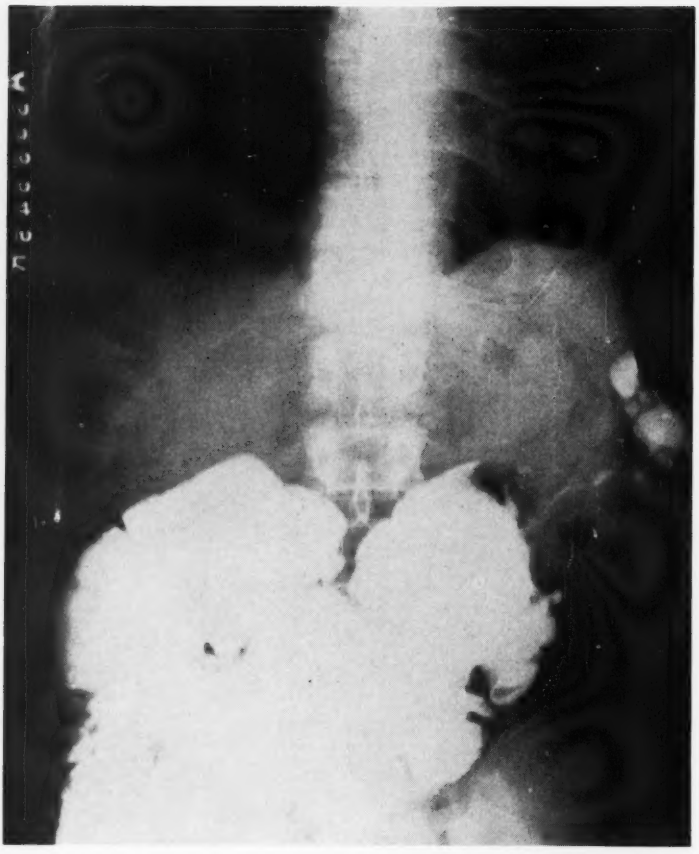


FIGURE 4: Roentgenogram following a barium enema, again demonstrating the lesion near the splenic flexure.

An exploratory operation was again performed, seventeen months after the gastric resection. The distal third of the transverse colon was involved in a metastatic omental mass. Several loops of small bowel were adherent in this area. Additional metastatic deposits were present throughout the abdomen. Iliosigmoidostomy beyond this obstruction was not feasible because obstruction high in the small intestine involved in the mass would soon ensue. The operative wound was closed.

The patient was discharged from the hospital on the eighteenth postoperative day, his condition unimproved.

THE DIAGNOSIS OF GOUT

RUSSELL L. HADEN, M.D.

Gout is the most commonly overlooked type of joint disease. The diagnosis usually is easy if the basic clinical picture is kept in mind; it is often made from the history alone. The typical subject is an obese, ruddy, otherwise healthy man, engaged in a sedentary occupation. The onset is very sudden, and the pain is very severe; usually only a single joint is involved at first. The pain often begins in the great toe joint or in the foot, and often begins at night. The affected joint is much swollen, very red and exquisitely tender. Early in the disease, attacks last from a few days to two weeks, with a gradual subsidence of symptoms. Following the acute attack the patient is absolutely free of all joint manifestations. The attacks almost always recur after some precipitating influence, such as an indiscretion in diet or the use of alcohol. With recurrences the same joint may be involved or the disease may appear in a single other joint or in several joints. In time the attacks are apt to last longer; finally, the disease may become chronic with marked joint deformity.

There are many variations of this fundamental typical picture. The disease may occur in women; the patient may not necessarily be healthy-looking; some other disease, such as leukemia or polycythemia, may precipitate an attack; the disease may run a chronic course from the onset; and any joint may be involved.

While there may be many different clinical pictures, gouty arthritis should be thought of as characterized by recurrent, acute attacks of very painful arthritis which clear up completely, leaving a normal joint between attacks early in the course of the disease.

The diagnosis of gout does not depend entirely upon the clinical history. Certain laboratory procedures help greatly. As a rule, the uric acid content of the blood is increased. However, the uric acid is frequently higher than normal in conditions other than gout. Rarely, the gout may be active without an increase in uric acid. The sedimentation rate is uniformly elevated when the disease is active. An elevated sedimentation rate is characteristic of rheumatoid arthritis also, so this finding may only be confusing. The roentgen findings, if typical, help greatly, but many active cases show no positive findings. The one absolute diagnostic criterion is the presence of the tophus. The most common site is in the margin of the lobe of the ear. A nodule should not be considered as a tophus, however, unless the needle-shaped sodium biurate crystals can be demonstrated in it.

To emphasize the clinical picture of gout, Dr. Jack Kinell and I have analyzed the findings in 100 cases studied completely at the

Cleveland Clinic. Only five of the patients were women. Most came from the highest social level. About 80 per cent were lawyers, merchants, executives and business men; 10 per cent were physicians.

Typically, the gouty patient is an obese, ruddy complexioned individual with an appearance of exceptional well-being. The average pounds overweight for the entire group was 31. Only two patients were underweight. Thirty per cent were 40 pounds or more overweight. Most of the patients had a red cell count and hemoglobin normal or above. These findings are in marked contrast to the almost constant anemia in other types of acute arthritis and in rheumatoid arthritis.

The average age of our patients when first seen was about 50 years, with an average duration of symptoms of seven years. The onset of the disease occurred between the ages of 33 and 50 years in 60 per cent of the cases.

A history of sudden, acute pain in a great toe is important in the diagnosis of gout. However, joints other than the great toe may be the site of the initial disturbance and, if so, may mislead the examiner. When any male patient presents himself with a story of acute, monarticular joint pain of sudden onset, consideration should be given to gout as a possible cause even though almost any joint other than the first metatarsophalangeal is the one involved. In our series the original joint affected was the great toe in 53 cases, the ankle in 13, and the foot in 12. After the onset of the disease almost every other joint in the body may be involved.

The question of hyperuricemia in gout is well established. During acute attacks, in the early stages of the disease, the level of the blood uric acid is usually, but not invariably, elevated. Therefore, with a typical history and with the type of individual in whom one might suspect gout, a diagnosis of gout need not necessarily be excluded by the finding of a blood uric acid of normal level. In the interim between attacks, the uric acid will very often not be elevated. Toward the end of the first stage, years after the onset of the disease, the likelihood of finding a hyperuricemia during and between attacks increases. When the stage of chronic gouty arthritis is reached, the level of uric acid in the blood is almost always high. The average blood uric acid for the entire group was 3.8 mg. per cent. The highest was 6 mg. in a patient with acute gout who had been having symptoms for nine years.

There is only one specific lesion of gout, namely, the tophus. A diagnosis of the condition before the appearance of tophi is often easily made but should be qualified by the designation presumptive or pretophaceous gout. Following the appearance of tophi, a diagnosis of proved or tophaceous gout may be applied. As hyperuricemia develops and as the disease becomes more chronic, the possibility of

demonstrating tophi is increased. However, the presence of tophi is an extremely variable finding. They are not as commonly found as is generally suspected. Furthermore, they may appear during any stage of the disease, with or without a chronic hyperuricemia, and often may not appear at all, although the disease may be of twenty or thirty years' duration, and although the blood uric acid may be decidedly high.

There were only 21 cases in this series in which tophi could be demonstrated. The duration of symptoms in these patients ranged from only two weeks to ten years. The patient with symptoms of only two weeks' duration must have had gout for a longer period of time than the history would indicate. The fact that tophi developed before the onset of joint symptoms is no more difficult to understand than the symptom-free interval between acute attacks which the patients typically show. No tophi were found in 13 cases with histories of from ten to thirty years' duration. Proved tophaceous gout may be present with a normal blood uric acid level.

Positive roentgen evidence of gout is usually lacking in early attacks. This is often disappointing since the symptoms and clinical findings are so striking. As the disease progresses, the possibility of positive findings by roentgen examination increases. Strangely enough, however, many cases show nothing by x-ray although the disease may have been present for several years and although there may have been repeated attacks of severe joint pain and swelling. When deformity results in the stage of permanent arthritis, roentgen changes are always present but may not have the so-called typical appearance of gout. Positive roentgen evidence of gout was found in only 25 cases.

Areas of erosion representing osseous tophi in articular or juxta-articular bone constitute the typical appearance of gout by x-ray. These may appear as destructive changes in articular surfaces or may show up as definite punched-out areas in the shaft of the bone. Often these areas are small and very similar to the changes found in degenerative or atrophic arthritis. Unless areas of erosion of this type are large, they cannot be directly attributed to gout but, if large, they are highly significant. However, it is apparent from the above data that roentgen evidence of gout, like the appearance of tophi and the finding of hyperuricemia, is variable and unreliable, especially during the early stages before chronic arthritic changes develop.

Tissues other than the joints are affected in gout. Vascular nephritis is common. Although a faint to heavy trace of albumin was found in the urine of about half of our patients, sufficient indication to warrant a study of kidney function was lacking. Only three patients had casts in the urine.

Renal stones are not uncommon. Although only 11 per cent of our patients had or gave a history of stone, a useful rule to follow as suggested by Hench is, "suspect gout in acute or chronic arthritis with a history or findings of renal colic or nephritis." This may be helpful at times in differentiating between rheumatoid arthritis and gout.

Bursitis or tendonitis may often be attributed to gout, but the proof of this depends upon the finding of other manifestations of the disease. Neuritis is a well-known complication.

The sedimentation rate may help greatly in making the diagnosis of gout, since it is uniformly elevated in acute cases and often in chronic cases. The average rate in the 100 cases reported here was 0.94 mm. per minute, while the upper limit of normal is 0.45 mm. The sedimentation rate varies with the clinical activity of the disease, although the blood uric acid does not.

It is apparent from this summary that the only constant findings in gout is the clinical pattern. The diagnosis cannot be excluded on a low uric acid level, on the absence of tophi, or on the absence of x-ray findings.

In treating patients with gout, weight reduction is most important if the patient is overweight. During an acute attack a purine-free diet should be used. The patient should always follow a low purine diet even in the absence of symptoms. Alcohol should be absolutely forbidden.

Colchicine will often abort or relieve an attack. Three to six tablets containing 1/120 grain of the alkaloid are given daily unless diarrhea develops. If there is no response to colchicine, cincophen may be necessary. The dangers of this drug have probably been overstressed.

Gout is a chronic metabolic disease, so is probably never cured. The patient must always reckon with the possibility of recurrence. Constant medication may prevent a recurrence. It is often necessary to continue indefinitely the use of colchicine or cincophen three days of each week.

THE TREATMENT OF ACUTE SUBACROMIAL BURSITIS

J. I. KENDRICK, M.D.

The onset of acute subacromial bursitis often is sudden. There may be a short prodromal period of soreness and aching in the shoulder, but the acute symptoms frequently develop within a period of a few hours. Preceding the onset of the symptoms may be a history of an injury to the shoulder, which may be insignificant or in the nature of a sudden twist or jerk. There may be no immediate pain, but soon after the injury symptoms of an acute subacromial bursitis may develop.

Pain and disability in the shoulder are the outstanding symptoms. The pain is acute and localized to the region of the anterolateral aspect of the shoulder, and often radiates to the side of the neck and region of the attachment of the deltoid muscle. There usually is marked restriction of motion in abduction and in internal and external rotation. Movements are restricted by marked muscle spasm and are associated with acute pain. A limited degree of painless flexion and extension usually is possible. Palpation reveals invariable tenderness over the subacromial region or over the greater tuberosity of the humerus. Occasionally the bursa may be distended.

Subacromial bursitis may occur as an acute serous bursitis or there may be flocculent calcific deposits in the bursa. I have observed several cases in which an acute process developed in a chronic case in which roentgenograms showed a dense calcific deposit in the bursa. This type of case responds well to aspiration and irrigation, but return to normal function is more prolonged.

TREATMENT

The needle aspiration and irrigation method of treatment of acute subacromial bursitis, described by Patterson and Darroch[1], is a simple and effective procedure. I shall describe certain technical points which have proved useful in carrying out this procedure.

The operation is done under local anesthesia. The tender spot beneath the acromion process or over the greater tuberosity is the invariable guide to the bursa. This tender spot is thoroughly injected with ¾ per cent novocaine solution, about 25 to 30 cc. being necessary to produce satisfactory anesthesia. A needle is then passed into the bursa and an attempt is made to aspirate material from it. In passing the needle into the bursa, the area of maximum tenderness is the best guide

and is more reliable than anatomic descriptions. Satisfactory irrigation may be carried out with one needle. In other cases, however, two needles may be used, the saline solution being introduced through one needle, and allowed to drain from the other needle. If dense calcification is present, it often can be broken apart with the point of the needle and can be washed out. If the bursa is difficult to aspirate because of a dense calcific deposit or because of flocculent material plugging the needle, the bursa may be punctured in several places, as suggested by Weeks and Delprat[2]. The results are almost as satisfactory as when the bursa can be aspirated thoroughly.

Treatment is greatly facilitated and recovery is hastened if the patient can be kept in the hospital for two or three days. Following operation the patient is placed in bed with the arm in traction in a position of 90 degrees abduction and 90 degrees external rotation. Ice caps are applied to the shoulder during the first twenty-four hours. Hot cloths are then applied for a period of one hour four times each day. After forty-eight hours, motion is fairly free and active exercise can be started. However, the exercises should be graduated so that soreness does not persist because of overactivity.

The period of disability will vary with the requirements placed upon the patient by his occupation. The period of disability for an office worker may be only a few days, while that of a laborer may extend to three weeks.

REFERENCES

1. Patterson, R. L. Jr. and Darroch, W.: Treatment of acute bursitis by needle irrigation, J. Bone & Joint Surg., 19:993-1002 (October) 1937.

2. Weeks, A. and Delprat, G. D.: Subdeltoid bursitis (acute), Internat. Clin. 3:40-48 (September) 1936.

LAURENCE-MOON-BIEDL SYNDROME

A Report of Four Cases in One Family

E. Perry McCullagh, M.D., and E. J. Ryan, M.D.

The Laurence-Moon-Biedl syndrome was first described by Laurence and Moon in the British Journal of Ophthalmology in 1866. Further reports by Bardet[1] in 1920 and by Biedl[2] in 1922 resulted in the application of the terms Biedl-Bardet syndrome and Laurence-Biedl syndrome in some instances. The condition is uncommon, only 129 cases having been reported until the middle of 1940, according to Schwartz and Boudreau[3].

The following features are characteristic of the condition: (1) Mental retardation, (2) pigmentary degeneration of the retina, (3) adiposogenital dystrophy, (4) familial occurrence, and (5) polydactylism or syndactylism. The presence of all of these characteristics is not a fundamental necessity in the establishment of the diagnosis, but when one or more is absent, a familial occurrence would appear to be a reasonable requirement, as mentioned by Molitch, et al.[4] Of the 77 cases (including 4 of their own) in the world literature until 1932, reviewed by Reilly and Lisser[5], only 25 presented all of the typical findings. Other anomalies have been reported by various observers, and include nystagmus, night blindness, atresia ani, various additional skeletel abnormalities, and deafness, among others.

The pathogenesis of the disorder is incompletely understood. The familial occurrence is significant. Numerous reports are available in which are recorded the finding of one or more characteristics of the condition in antecedents of affected individuals. There have been no instances reported indicating inheritance of the entire complex, although, as mentioned by Sorsby, Avery and Cockayne[6], there have been case records which indicate that patients with this syndrome may not necessarily be sterile. Biedl[2] considered the disorder to be due to a diencephalic lesion. Raab[7] suggested that a high or massive dorsum sellae might cause pressure on the infundibular stalk, thus disturbing the passage of secretion from the posterior lobe of the hypophysis to the floor of the third ventricle. This theory is no longer tenable. Ornsteen[8] stated: "The frequent association of the first three elements of the syndrome (adiposogenital dystrophy, retinitis pigmentosa, and mental deficiency) is explained on the basis of a developmental defect of the ectopic zone of the prosencephalon, for the embryological reason that the hypothalamus (infundibulum) and the optic chiasm take origin from the ventral segment of the ectopic zone of Schulte. The other developmental anomalies . . . . . appear because of the coupling of

somatic genotypic defect characters with the cerebral unit characters mentioned above". Cockayne, Krestin, and Sorsby[9] and Jenkins and Poncher[10] suggested that the syndrome is due to a linkage of two or more genes bearing unit characters. These genes may bear simple recessives but cannot carry simple dominants. Cockayne, et al.[9] give priority in this opinion to Rieger and Trauner[11], who felt that the parts of the syndrome based on mesoblastic and epiblastic defects are recessive and result from mutations of 2 genes in the same chromosome. Macklin[12] stated that the complete syndrome, "may be dependent upon two factors, both of which are necessary before the disease becomes evident, one of which is dominant and autosomal, and the other sex-linked recessive". Marmor and Lambert[13] feel that the weight of evidence points to the fact that the pigmentary retinal degeneration in the Laurence-Moon-Biedl syndrome is a congenital anomaly dependent upon an inherited chromosal factor, and they state further that this points toward the congenital nature of the usual form of retinitis pigmentosa. Hecker and Warren[14] believe that the mental deficiency is of primary importance, a result of defective germ plasm in the antecedents, and that the other changes are secondary through involvement of the hypothalamus and indirectly the hypophysis. The polydactylism or other skeletal defect is considered to be another manifestation of defective germ plasm.

Complete pathologic study by Griffiths[15], including careful examination of the endocrine system and serial sections of the brain from the anterior part of the chiasm to the midbrain, showed no lesion which could be considered causative.

The treatment for this condition has been widely variable, and numerous endocrine preparations have been used. On the whole, the results, for obvious reasons, have not been very satisfactory. The persistent use of thyroid extract has seemed most beneficial. Weight reduction might profitably be encouraged by a fixed low calorie diet.

Because of the relatively uncommon occurrence of the condition, we wish to report four cases which occurred in one family. A few such occurrences have been reported previously.

The parents in these cases are native born Italians who have lived in this country for thirty-six years. The mother is the first cousin of the father. As nearly as could be determined, there had been no other intermarriages, and there was no history of blindness or obesity in previous generations. The father was well developed and was healthy except for arterial hypertension, the blood pressure being 185 mm. systolic and 120 mm. diastolic. The mother was an obese, healthy woman, 35 years of age. A sister of the mother was normal. Of the five children, all male, in the family, only one was normal. The normal sibling was the second son (Fig. 1, B).

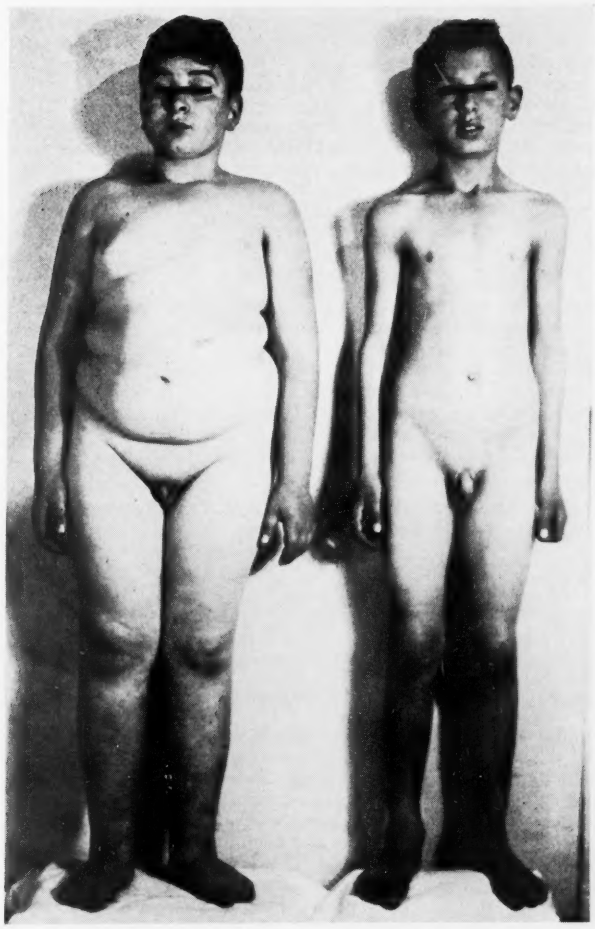


FIGURE 1: A. Case 1. B. Normal brother.

Case 1 (*Fig. 1, A*): The first patient was a boy, 6 years of age, who was seen first in 1926, complaining of "loss of vision" which had been progressive since infancy. He was the first child, was delivered by instruments, and weighed 7 pounds (3.2 Kg.) at birth. At the age of 4 months he had had a severe furunculosis which lasted about a month. He first walked at 19 months of age. The age at which he first talked could not be determined. When one year old he weighed 22 pounds (10 Kg.). When the patient was 5 months old, the mother noticed that he passed a larger amount of urine than did the other children at the same age. When 3 years old he had a diurnal somnolence, and an associated insomnia. From the age of 4 to 6 years, he frequently complained of headaches, and his mother noticed for the first time that he was gaining weight rapidly, although the exact amount could not be determined.

Physical examination revealed a 6 year old boy who weighed 73 pounds (33.8 Kg.), and was 44 inches (111.8 cm.) tall. No abnormalities were noted about the head and neck. The thyroid gland was not enlarged. The heart and lungs were normal, as was the abdomen, except for the obesity. The genitalia were thought to be normal, although the penis appeared small because of prominence of the mons pubis. The skin was dry. The hands were chubby and obese, with very definite tapering of the fingers. There was no polydactylism or syndactylism. Vertical and rotary nystagmus were present in both the right and the left eyes. A completely satisfactory examination of the retina could not be made because of the nystagmus, but diffuse pigmentary degeneration of the retina with optic atrophy was demonstrated. Both patellar and Achilles reflexes were absent. A roentgenogram of the skull showed a normal sella turcica. Five grains of whole pituitary gland three times a day were prescribed, but apparently the medication was not taken.

The family was not seen again until four years later. At that time the patient's pupils were found to be dilated, and a considerable degree of nystagmoid movement was present in both the vertical and the horizontal axis. The retina had a salt and pepper appearance. Although there was no red spot in the macula, there was definite central macular disturbance. There was an appearance as of diffuse chorioretinitis and a secondary optic atrophy. A roentgenogram of the skull was repeated and the sella turcica again was reported to be normal. The basal metabolic rate was minus 29 per cent. The glucose tolerance was normal and the Wassermann test of the blood gave a negative reaction.

The family was not seen again until December, 1933, three years after the second examination. Efforts to have them return for complete studies and treatment had been fruitless, so a journey was made to their home, where the entire family was seen. This examination revealed that the disease had progressed considerably in the three years. The patient was a large, heavy, mentally dull boy 12 years of age. He slept most of the time. He complained of occasional vertical headaches. There was no polydipsia or polyuria. His appetite was excessive, but he did not eat between meals, although he did manifest an increased desire for sweets. It was quite obvious that he was even more mentally subnormal than could be due to the handicap of blindness. He was reticent about talking, but when he talked his words were poorly formed and incomplete.

At the time of this examination the patient weighed 160 pounds (72.7 Kg.). His height was 58¼ inches (148 cm.), and his span was 61⅜ inches (155.9 cm.). The blood pressure was very unstable. When first taken it varied from 134 mm. systolic and 100 mm. diastolic, to 140 mm. systolic and 90 mm. diastolic. The pulse rate was not elevated. The body contours showed feminine characteristics. The obesity was generalized, but there was a preponderance of the girdle and mammary distribution. The skin was very dry, especially over the arms and legs where it was scaly and almost ichthyotic. The hair of the scalp was short, coarse, and straight. There was a marked malar flush. The eyes showed vertical and rotary mystagmus so that retinal examination was not entirely satisfactory. In addition to the changes noted three years previously, there was some pigmentary degeneration about the nerve head. The teeth were in good condition. There was some spacing of the upper and lower teeth. The tonsils had been removed, but small tags remained on both sides. There was no lymphadenopathy in the cervical, axillary, epitrochlear, or inguinal regions. The thyroid gland was barely palpable. The chest was short and thick. The breasts, which were chiefly fat, were the size of those of a 16 year old girl. The areolae were larger than those of the average male. Stimulation of the areola or nipple produced erection and wrinkling. The lungs were normal to percussion and auscultation. The cardiac outline was normal. The second aortic sound was accentuated but there were no murmurs. The peripheral vessels were soft. The abdomen was obese and pendulous. It measured 44 inches (111.8 cm.) around the largest diameter. There was a flat, pigmented nevus of the vascular type about 5 x 3 cm. in area on the lower left abdominal quadrant. No abnormal organs or masses were palpable. The distance from the top of the symphysis pubis to the tip of the penis measured 3 inches (7.6 cm.), although the penis did not appear to be more than one inch in length because of the overlying fat. The testes were in the scrotum and felt quite normal. The hands were short, pudgy and thick, with marked tapering of the fingers. The legs were of the

barrel type with large ankles. The deep tendon reflexes of the upper extremities were very sluggish. The patellar and Achilles reflexes could not be obtained.

A concentrated morning specimen of urine was obtained, and a Friedman test was done. This showed no excess of gonadotropic substance.

In 1932, when the patient's chronologic age was 11 years, his mental acuity had been studied in anticipation of entering Braille classes, and his mental age was estimated to be 5 years.

Case 2 (Fig. 2): Cases 2 and 3 are twins. This patient was first seen in 1930 at the age of 6 years. The complaints were blindness and obesity. His birth weight was not known. He was delivered by instruments and was a normal baby. Development was apparently normal until the age of one year, when the patient began to gain weight rapidly. No complaint of headache was made. Impairment of vision was noted during the first year of life. Polyphagia had been observed, but there had been no polyuria, polydipsia or somnolence.

Physical examination revealed marked obesity, and the body configuration was feminine. The skin was dry, especially over the anterior parts of the legs. The hair was of normal texture. The thyroid gland was not palpable. The genitalia were developed normally for the age. The fingers tapered slightly. Examination of the eyes revealed findings similar to those in the first case, except that there was a more marked, diffuse chorioretinitis in the left eye, and there was a dark, pigmented area about the macula. There was neither polydactylism nor syndactylism. A roentgenogram revealed the sella turcica to be small, but normal.

When the patient was next seen three years later, in December, 1933, he was an active, alert boy, but of less than average mentality. There was some polyphagia and an increased liking for sweets, but no polydipsia or polyuria. He complained of occasional vertical headaches. His speech was broken and jerky. The words were very poorly formed and it was difficult to understand him. All of the affected boys demonstrated this same faulty enunciation which could be attributed in some degree to the fact that Italian was the only language spoken in the household, and English had been learned only during a year and a half of tutoring in Braille. Their speech was not the dysarthric type.

At the time of the examination in 1933, when 9 years of age, the patient was 58¼ inches (148 cm.) tall, weighed 124 pounds (56.4 Kg.), and had a span of 59⅜ inches (150.8 cm.). Abnormal fat deposits were present about the trochanteric and mammary areas, although there was a generalized obesity. The skin was very dry all over the body. There was a malar flush. The condition of the eyes was essentially the same as in 1930, but there was some increase in pigmentary degeneration. A vertical and horizontal nystagmus was present. The upper teeth were slightly spaced. One molar had erupted bilaterally and a second molar was partially erupted on the right and fully erupted on the left side. The tonsils had been removed. The thyroid gland was barely palpable. There was no lymphadenopathy. The chest measured 32 inches (76.2 cm.) at rest. The heart and lungs were normal. The second aortic sound was accentuated. The blood pressure was 124 mm. systolic and 95 mm. diastolic. The abdomen was obese and measured 37 inches (94 cm.) at its greatest circumference. There were no abnormal masses or organs. Measurement from the pubis to the floor was 30½ inches (77.5 cm.); from the tip of the penis to the edge of the symphysis pubis was 2⅛ inches (5.4 cm.). The penis appeared normal. The testes were small and lay in the scrotum. There was a scant beginning of pubic hair. No axillary hair was seen. The patient had the same type of thick hand with tapering fingers as did the other affected members of the family. The legs were of the barrel type. The reflexes were all present and normal. Urinary prolan was not increased as judged by the Friedman test. The mental age of this boy at the age of 8 was estimated to be 5 years.

Case 3 (Fig. 3): This patient was first seen in 1930 when he was 6 years of age. His birth had been by instrument delivery and the birth weight was not known. His development had been the same as that of his twin brother (Case 2). At the age of 5 years, he accidently shot himself with a 32 caliber revolver. The bullet entered the left orbit, de-

Physical examination revealed a 6 year old boy who weighed 73 pounds (33.8 Kg.), and was 44 inches (111.8 cm.) tall. No abnormalities were noted about the head and neck. The thyroid gland was not enlarged. The heart and lungs were normal, as was the abdomen, except for the obesity. The genitalia were thought to be normal, although the penis appeared small because of prominence of the mons pubis. The skin was dry. The hands were chubby and obese, with very definite tapering of the fingers. There was no polydactylism or syndactylism. Vertical and rotary nystagmus were present in both the right and the left eyes. A completely satisfactory examination of the retina could not be made because of the nystagmus, but diffuse pigmentary degeneration of the retina with optic atrophy was demonstrated. Both patellar and Achilles reflexes were absent. A roentgenogram of the skull showed a normal sella turcica. Five grains of whole pituitary gland three times a day were prescribed, but apparently the medication was not taken.

The family was not seen again until four years later. At that time the patient's pupils were found to be dilated, and a considerable degree of nystagmoid movement was present in both the vertical and the horizontal axis. The retina had a salt and pepper appearance. Although there was no red spot in the macula, there was definite central macular disturbance. There was an appearance as of diffuse chorioretinitis and a secondary optic atrophy. A roentgenogram of the skull was repeated and the sella turcica again was reported to be normal. The basal metabolic rate was minus 29 per cent. The glucose tolerance was normal and the Wassermann test of the blood gave a negative reaction.

The family was not seen again until December, 1933, three years after the second examination. Efforts to have them return for complete studies and treatment had been fruitless, so a journey was made to their home, where the entire family was seen. This examination revealed that the disease had progressed considerably in the three years. The patient was a large, heavy, mentally dull boy 12 years of age. He slept most of the time. He complained of occasional vertical headaches. There was no polydipsia or polyuria. His appetite was excessive, but he did not eat between meals, although he did manifest an increased desire for sweets. It was quite obvious that he was even more mentally subnormal than could be due to the handicap of blindness. He was reticent about talking, but when he talked his words were poorly formed and incomplete.

At the time of this examination the patient weighed 160 pounds (72.7 Kg.). His height was 58¼ inches (148 cm.), and his span was 61⅜ inches (155.9 cm.). The blood pressure was very unstable. When first taken it varied from 134 mm. systolic and 100 mm. diastolic, to 140 mm. systolic and 90 mm. diastolic. The pulse rate was not elevated. The body contours showed feminine characteristics. The obesity was generalized, but there was a preponderance of the girdle and mammary distribution. The skin was very dry, especially over the arms and legs where it was scaly and almost ichthyotic. The hair of the scalp was short, coarse, and straight. There was a marked malar flush. The eyes showed vertical and rotary mystagmus so that retinal examination was not entirely satisfactory. In addition to the changes noted three years previously, there was some pigmentary degeneration about the nerve head. The teeth were in good condition. There was some spacing of the upper and lower teeth. The tonsils had been removed, but small tags remained on both sides. There was no lymphadenopathy in the cervical, axillary, epitrochlear, or inguinal regions. The thyroid gland was barely palpable. The chest was short and thick. The breasts, which were chiefly fat, were the size of those of a 16 year old girl. The areolae were larger than those of the average male. Stimulation of the areola or nipple produced erection and wrinkling. The lungs were normal to percussion and auscultation. The cardiac outline was normal. The second aortic sound was accentuated but there were no murmurs. The peripheral vessels were soft. The abdomen was obese and pendulous. It measured 44 inches (111.8 cm.) around the largest diameter. There was a flat, pigmented nevus of the vascular type about 5 x 3 cm. in area on the lower left abdominal quadrant. No abnormal organs or masses were palpable. The distance from the top of the symphysis pubis to the tip of the penis measured 3 inches (7.6 cm.), although the penis did not appear to be more than one inch in length because of the overlying fat. The testes were in the scrotum and felt quite normal. The hands were short, pudgy and thick, with marked tapering of the fingers. The legs were of the

barrel type with large ankles. The deep tendon reflexes of the upper extremities were very sluggish. The patellar and Achilles reflexes could not be obtained.

A concentrated morning specimen of urine was obtained, and a Friedman test was done. This showed no excess of gonadotropic substance.

In 1932, when the patient's chronologic age was 11 years, his mental acuity had been studied in anticipation of entering Braille classes, and his mental age was estimated to be 5 years.

Case 2 (Fig. 2): Cases 2 and 3 are twins. This patient was first seen in 1930 at the age of 6 years. The complaints were blindness and obesity. His birth weight was not known. He was delivered by instruments and was a normal baby. Development was apparently normal until the age of one year, when the patient began to gain weight rapidly. No complaint of headache was made. Impairment of vision was noted during the first year of life. Polyphagia had been observed, but there had been no polyuria, polydipsia or somnolence.

Physical examination revealed marked obesity, and the body configuration was feminine. The skin was dry, especially over the anterior parts of the legs. The hair was of normal texture. The thyroid gland was not palpable. The genitalia were developed normally for the age. The fingers tapered slightly. Examination of the eyes revealed findings similar to those in the first case, except that there was a more marked, diffuse chorioretinitis in the left eye, and there was a dark, pigmented area about the macula. There was neither polydactylism nor syndactylism. A roentgenogram revealed the sella turcica to be small, but normal.

When the patient was next seen three years later, in December, 1933, he was an active, alert boy, but of less than average mentality. There was some polyphagia and an increased liking for sweets, but no polydipsia or polyuria. He complained of occasional vertical headaches. His speech was broken and jerky. The words were very poorly formed and it was difficult to understand him. All of the affected boys demonstrated this same faulty enunciation which could be attributed in some degree to the fact that Italian was the only language spoken in the household, and English had been learned only during a year and a half of tutoring in Braille. Their speech was not the dysarthric type.

At the time of the examination in 1933, when 9 years of age, the patient was 58¼ inches (148 cm.) tall, weighed 124 pounds (56.4 Kg.), and had a span of 59⅜ inches (150.8 cm.). Abnormal fat deposits were present about the trochanteric and mammary areas, although there was a generalized obesity. The skin was very dry all over the body. There was a malar flush. The condition of the eyes was essentially the same as in 1930, but there was some increase in pigmentary degeneration. A vertical and horizontal nystagmus was present. The upper teeth were slightly spaced. One molar had erupted bilaterally and a second molar was partially erupted on the right and fully erupted on the left side. The tonsils had been removed. The thyroid gland was barely palpable. There was no lymphadenopathy. The chest measured 32 inches (76.2 cm.) at rest. The heart and lungs were normal. The second aortic sound was accentuated. The blood pressure was 124 mm. systolic and 95 mm. diastolic. The abdomen was obese and measured 37 inches (94 cm.) at its greatest circumference. There were no abnormal masses or organs. Measurement from the pubis to the floor was 30½ inches (77.5 cm.); from the tip of the penis to the edge of the symphysis pubis was 2⅛ inches (5.4 cm.). The penis appeared normal. The testes were small and lay in the scrotum. There was a scant beginning of pubic hair. No axillary hair was seen. The patient had the same type of thick hand with tapering fingers as did the other affected members of the family. The legs were of the barrel type. The reflexes were all present and normal. Urinary prolan was not increased as judged by the Friedman test. The mental age of this boy at the age of 8 was estimated to be 5 years.

Case 3 (Fig. 3): This patient was first seen in 1930 when he was 6 years of age. His birth had been by instrument delivery and the birth weight was not known. His development had been the same as that of his twin brother (Case 2). At the age of 5 years, he accidently shot himself with a 32 caliber revolver. The bullet entered the left orbit, de-

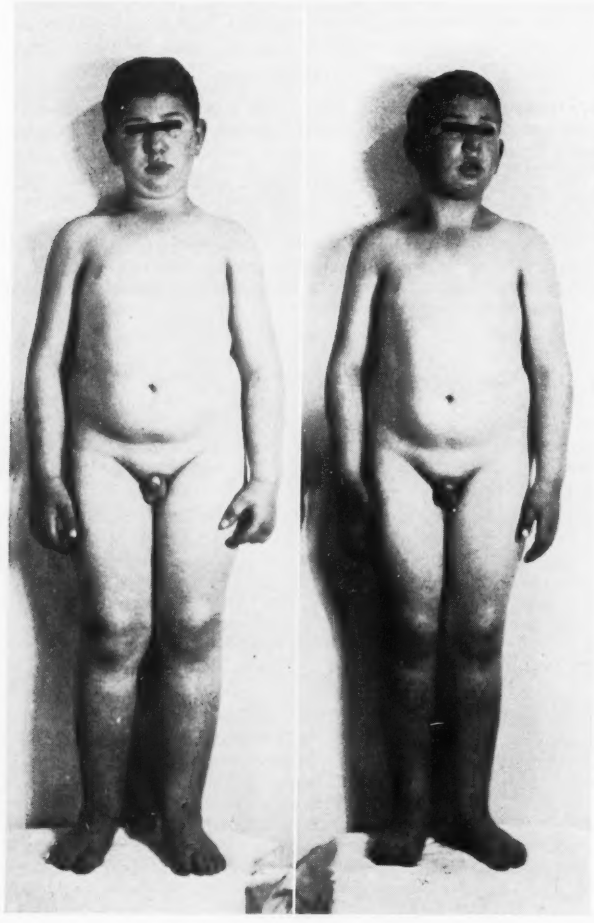


FIGURE 2: Case 2. FIGURE 3: Case 3.

stroyed the iris, and was reputed to have lodged in his skull, but a roentgenogram of the skull did not reveal it and no operative procedure had been performed.

The height was 48 inches (122 cm.). His body contour was essentially the same as that of his twin except that he was somewhat smaller. The fat deposits were of the female distribution. The thyroid gland was not palpable. The skin was normal. No secondary growth of hair was present. There was considerable degree of redness of the macular area of the right eye which was more marked than that of Case 1. In the left eye was a traumatic cataract. Neither polydactylism nor syndactylism was present. The basal metabolic rate was minus 25 per cent.

When the patient was seen in 1933, at the age of 9 years, he was alert and active, although there was some evidence of decreased mental capacity. There was a slight polyphagia and craving for sweets, but there was no polydipsia or polyuria. He com-

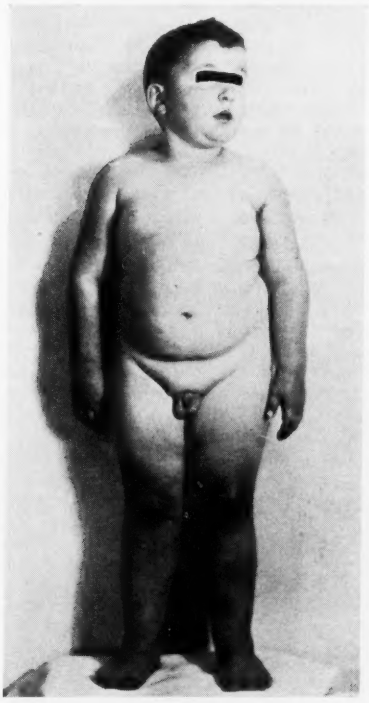


FIGURE 4: Case 4.

plained of occasional vertical headaches. He was 57 inches (144.8 cm.) tall, weighed 126 pounds (57.3 Kg.) and his span was 57¾ inches (146.7 cm.). The skin was very dry. The malar flush was prominent. There was a vertical and rotary nystagmus. The macular hyperemia was not noted at this time, but there was an increase of pigmentation about the nerve head. The tonsils had been removed. The teeth looked sound, although the first and second lower premolars were not completely erupted. The upper teeth were only partially erupted and all were spaced. There were no upper second molars. The thyroid gland was not palpable. The chest was short and thick. The nipples were not enlarged. The areolae were of normal male type. There were no significant abnormalities of the lungs or heart, although the second aortic sound was accentuated. The blood pressure was 134 mm. systolic and 96 mm. diastolic. The abdomen was obese and the mons pubis was prominent. The greatest circumference of the abdomen was 36½ inches (93.7 cm.). No abnormal masses or organs were present. The genitalia appeared normal. From the pubis to the floor measured 30¼ inches (76.8 cm.). From the inferior border of the pubis to the tip of the penis measured 2½ inches (6.4 cm.). The testes were small and lay in the scrotum. The reflexes were sluggish. There was an early growth of pubic hair but no axillary hair was present. The hands and feet were similar to those of the brothers. Urinary prolan was not increased according to the Friedman test. When his chronologic age was 8 years, he had attained an age of 6 years by mentality tests.

Case 4 (*Fig. 4*): This patient was 5 years old when seen in 1930. He was delivered by instruments and was a normal infant. There was no history of childhood convulsions or

injuries. He did not complain of headaches. Blindness had been progressive since the age of one year. Examination revealed a marked obesity which gradually had increased since the age of 2 years. It was particularly noticeable about the abdomen and the mammary and trochanteric areas. The skin was very fine, and was relatively but not entirely hairless. The head hair was normal. There was no somnolence, polyphagia, polydipsia or polyuria. The teeth were not spaced. The thyroid gland was palpable. The genital development was normal and the testes were in the scrotum. The hands were very short with tapered fingers. Examination of the eyes showed diffuse chorioretinitis, disc changes as seen in the other boys, and changes of a secondary type in the retinas. Polydactylism and syndactylism were absent. The sella turcica was of the normal size and shape.

When the patient was seen three years later, when 8 years old, he presented the same body build, malar flush, and dry skin that his brothers did, but to a lesser degree. He was the most alert and inquisitive of the group. He had the same speech difficulty and mental deficiency that the others exhibited. He weighed 100 pounds (45.5 Kg.) and was 50¼ inches (127.6 cm.) tall. The scalp hair was the same coarse, straight type. The upper teeth were spaced. Both lower second premolars were carious. The first lower, right premolar had been extracted and the second molars had not erupted. All the upper teeth except the central incisors were incompletely erupted or at least very short. The tonsils were present and were not diseased. The chest was small. The nipples and areolae were not enlarged. The heart and lungs were normal. The blood pressure was 134 mm. systolic and 90 mm. diastolic. The abdomen was obese and there were no palpable abnormal masses or organs. The genitalia were small. From the anterior border of the symphysis pubis to the tip of the penis measured approximately 1 1/5 inches (3.8 cm.). From the pubis to the floor measured 25½ inches (64.8 cm.). The hands and legs were the same as seen in the other brothers. The reflexes were all present and active. There was vertical and rotary nystagmus. The fundi were pale. The nerve head was pale and covered with, or had the appearance of, a black granular pigment. Urinary prolan was not increased, as judged by the Friedman test.

DISCUSSION AND SUMMARY

Four cases of the Laurence-Moon-Biedl syndrome are presented; first, because of the relative rarity of the condition; and second, because of the still less frequent occurrence of the syndrome in four members of the same family. The diagnosis has been well established by the presence of four of the five cardinal symptoms in each case, the only one lacking being the polydactylism. This was excluded by roentgenologic study, as well as by clinical examination. It might also be mentioned that in these, as in other reported cases, a deficiency in development of the genitalia in the presence of marked obesity, may often be more apparent than real, and that a diagnosis of hypogonadism often is exceedingly difficult before the age of puberty. Parental consanguinity, as reported here, is frequent in the Laurence-Moon-Biedl syndrome.

REFERENCES

1. Bardet, G.: Thése de Paris, 107,470, 1920.

2. Biedl, A., Deutsche med. Wchnschr., 48:1630, 1922.

3. Schwartz, R. C., and Boudreau, E. M.: Laurence-Moon-Biedl syndrome without polydactylism but with syndactylism; Report of a case, Arch. Ped., 57:520-524, (August) 1940.

4. Molitch, M., Gladen, R. G., and Pigott, A. W.: Laurence-Moon-Biedl syndrome, Report of three cases, Endocrinol. 19:682-688, (November-December) 1935.

5. Reilly, W. A., and Lisser, H.: Laurence-Moon-Biedl syndrome, Endocrinol, 16:337-357, (July-August) 1932.

6. Sorsby, A., Avery, H., and Cockayne, E. A.: Obesity, hypogenitalism, mental retardation, polydactyly, and retinal pigmentation. The Laurence-Moon-Biedl syndrome, Quart. J. Med., 8:51-68, (January) 1939.

7. Raab, W.: Klinische und röntgenologische Beiträge zur hypophysären und zerebralen Fettsucht und Genitolatrophie, Wien. Arch. f. inn. Med., 7:443-530, 1924.

8. Ornsteen, A. M.: A contribution to the pathogenesis and heredity of the Laurence-Biedl syndrome (dystrophia adiposogenitalis, retinitis pigmentosa, mental deficiency, and polydactylism), Am. J. M. Sc., 183:256-268, (February) 1932.

9. Cockayne, E. A., Krestin, D., and Sorsby, A.: Obesity, hypogenitalism, mental retardation, polydactyly, and retinal pigmentation, The Laurence-Moon-Biedl Syndrome, Quart. J. Med., 4:93-120, (April) 1935.

10. Jenkins, R. L., and Poncher, H. G.: Pathogenesis of the Laurence-Biedl syndrome, Am. J. Dis. Child, 50:178-186, (July) 1935.

11 Rieger H., Trauner, R.: Ueber einen Fall von Biedl—Bardet—schem Syndrom und die Erblichkeitsverhaltnisse dieses Zustandes, Ztschr, f. Augenh., 68:235-243, (July) 1929.

12. Macklin, M. T.: Laurence-Moon-Biedl syndrome: Genetic Study, J. Hered., 27:97-104, (March) 1936.

13. Marmor, J., and Lambert, R. K.: Laurence-Moon-Biedl syndrome. Its relation to general problem of retinitis pigmentosa, Arch. Int. Med., 61:523-536, (April), 1938.

14. Hecker, A. O. and Warren, V. C.: Girdle type adiposity among mentally deficient males, Am. J. Dis. Child, 54:1257-1271, (December) 1937.

15. Griffiths, G. M.: Laurence-Moon-Biedl syndrome, A pathological report, J. Neurol & Psychiat., 1:1-4, (January) 1938.

THE VITAMINS AND SEX HORMONES CONCERNED IN REPRODUCTION

D. ROY McCULLAGH, Ph.D.

The vitamins, the hormones, and the enzymes constitute three important groups of substances of special interest to the biological chemist. Although many of the more startling discoveries in these fields seem already to have been made, our knowledge remains exceedingly elementary. Little is known about the details of the mechanism by means of which these substances are effective, and only recently has any considerable interest been evinced concerning their interrelationship. In a recent review, Bernheim[1] mentioned several interesting examples of the interaction of vitamins and cell catalysts.

The purpose of the present review is to summarize some of the effects of nutritional states on the reproductive organs, and in some cases, to compare and contrast endocrine and vitamin deficiencies. Most of the available information has been the result of work with the rat, and some of the facts presented here may not be applicable to man. Mason[2] recently considered this subject in a comprehensive review, and the reader is referred to his extensive bibliography.

The hormones and the vitamins are closely related in many respects, and both words have been used so extensively that their meanings are no longer very closely defined. For the purpose of this discussion, both may be considered as organic substances necessary for normal health; the vitamins are exogenous, whereas the hormones are endogenous. Depending upon the biological system being considered, some substances may fall into either group. For example, thiamin (vitamin B_1) must be considered as a hormone in plants and as a vitamin in animals. In man, hexuronic acid (vitamin C) is an essential exogenous substance and hence a vitamin, whereas in the rat it is made within the tissues and would therefore be a hormone.

THE TESTES

The male gonads are known to serve two functions: (1) spermatogenesis and (2) the production of one or more hormones. It is also known that both of these functions cease following hypophysectomy and that they can be maintained by injections of extracts of the pituitary gland. Some investigators believe that there are two pituitary gonadotropic hormones, one stimulating spermatogenesis and the other stimulating the interstitial cells of the testes to the production of androgenic material. The androgens or male hormones, in turn, play a role in the

maintenance of the normal anatomy and function of the penis and secondary sex glands, and male sex characteristics. They also probably serve some function in stimulating spermatogenesis, since spermatogenesis continues after hypophysectomy if androgens are supplied. The androgens also have numerous profound metabolic effects.

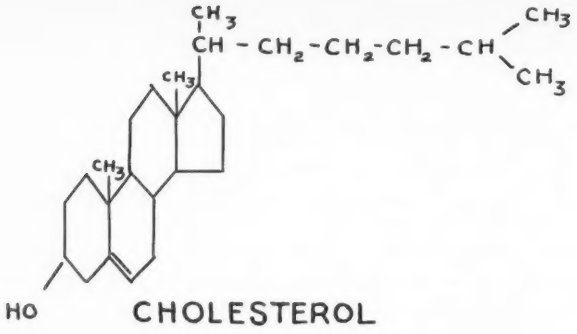
The male hormonal mechanism is controlled in such a way that the production of the various hormones is very flexible and the testes will function normally under a great variety of conditions. The flexibility is attained through a delicately balanced reciprocal relationship between the testes and the pituitary gland. The testes depress the pituitary gland and the latter stimulates the testes. Therefore, hypofunction of the testes results in increased pituitary activity and hence a return to normal. However, deficiencies of certain vitamins will completely disturb testicular function.

Vitamin A, which is a fat soluble carotinoid substance, and the lack of which results in poor growth, xerophthalmia, night blindness, etc., is very essential for proper testicular function. In the vitamin A deficient animal, spermatogenic activity is greatly reduced. In mild deficiency, spermatozoa are not produced, but several layers of spermatogonia and spermatocytes may exist. In extreme deficiency, only a few germ cells remain and the interstitial cells remain almost normal. In the rat, the degeneration of the testes which occurs after severe vitamin A deficiency can readily be cured in a period of about two months. This cure can be effected if adequate vitamin is added to even a very low caloric diet.

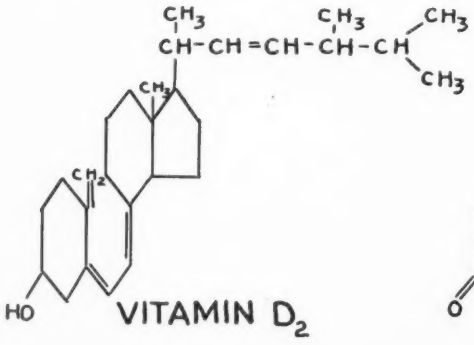
Until further researches have been accomplished, the *vitamin B complex*, in most cases, will have to be considered as a whole. Vitamin B_1 is necessary for testicular function in birds. Studies in the pigeon and the domestic fowl demonstrate profound testicular degeneration in vitamin B deficiency. This is not the result of inanition and can be cured by adding vitamin B to the diet for a period of less than a month. The picture is definitely different in mammals in that in vitamin B deficiency the testes remain almost normal. Any changes which occur can be attributed to loss of appetite with resulting inanition. Chinese coolies have been reported dying of beriberi without any considerably injury to the testes.

It has not been clearly demonstrated whether *vitamin C* deficiency directly influences testis function. The general condition of the scorbutic animal or man, of course, renders him less capable of reproductive activity. Normally, there is a high concentration of vitamin C in the testes, as is the case in other glandular material. However, it seems to have no direct relationship to the hormones in male or female animals.

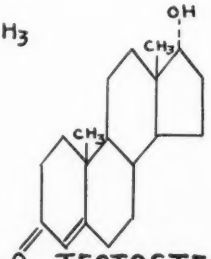
Vitamin D, the antirachitic hormone, is chemically closely related to cholesterol, as are the androgens, the estrogens, and progesterone. It is not impossible that cholesterol is the precursor of vitamin D and also



CHOLESTEROL



VITAMIN D_2



TESTOSTERONE

of the hormones mentioned above. The structural formulas given in figure 1 demonstrate the close relationship between cholesterol, vitamin D_2, and testosterone. Certain of the adrenal hormones and the ovarian hormones are also of this steroid configuration.

It is unnecessary here to review the relationship of vitamin D to the metabolism of calcium and phosphorus. That normal calcification will not occur without this vitamin is well established. Descriptions of the disturbances of mineral metabolism and of the rickety skeleton are available in many standard works. Although vitamin D deficiency does not appear to cause any testicular injury, this vitamin is related in function to the testes in that the androgens also influence bone growth. Following castration or in hypogonadism from other causes, skeletal calcification is normal insofar as calcium deposition and bone composition is concerned. However, normal skeletal maturation does not occur, as evidenced by delayed epiphyseal closure. As a result, the long bones usually continue to grow for an abnormally long period. In the human this results in an individual whose arms and legs are long in proportion to his torso.

Vitamin E: The existence of this vitamin has been known for nearly twenty years, and it recently has been shown to be alphatocopherol. In vitamin E deficiency is seen the most profound testicular tubular damage producable by any nutritional deficiency. At the same time the interstitial cells remain intact and the experimental animals remain vigorous without other untoward symptoms. If the deficiency is mild, the only noticeable symptom may be sterility. As the deficiency becomes more severe, the sperms change in morphology and staining characteristics and eventually disappear from the semen. In complete deficiency, the germinal epithelium gradually undergoes lysis and other forms of degenerative changes until it liquefies or is sloughed off into the epididymis. The tubular content is then limited to a syncytial Sertoli mass. These histologic changes are usually accompanied by loss of sex interest.

In the rat the testicular damage seen in vitamin E deficiency differs from other similar changes, in that it not only is more profound but also is completely irreparable. Once the rat is depleted of vitamin E, and before morphologic changes have more than commenced, the addition of vitamin E to the diet will not prevent destruction, nor will it produce a return of spermatogenesis.

The reaction of the rat to vitamin E deficiency is of considerable importance in interpreting the endocrinologic findings concerning testis-pituitary interrelationships. Following castration, the pituitary gland undergoes certain functional and morphologic changes. The basophilic cells, in particular, are altered and the gonadotropic potency of the whole gland increases, as indicated by assay of the glandular material using immature animals. Very similar, if not identical, changes appear in the pituitary glands of vitamin E deficient animals. In vitamin E deficiency the interstitial cells which produce the male sex hormone, are morphologically and functionally intact, as indicated by the condition of the secondary sex glands. It is possible, therefore, to argue that in both vitamin E deficiency and castration the changes in the pituitary gland are the result of destruction or removal of the tubular portion of the testes. These, and many other considerations, have led to the postulation of a testicular hormone other than the androgens. Indeed, several workers have effectively used nonandrogenic testicular extracts to prevent the castration changes in the pituitary gland. The hypothetical pituitary hormone which is thought to depress the pituitary gland is known as inhibin. In this laboratory large quantities of testicular concentrates which act as sexual depressants have been made. Attempts to isolate inhibin are now in progress.

The picture of testicular physiology depicted above, however, is complicated by certain known facts. Among these is that several of the androgens (testosterone, testosterone propionate, and dehydro-

androsterone) have been definitely shown to maintain normal function and morphology in the pituitary gland of the castrated rat. Also, the testes are known to contain estrogens, which also have a direct effect upon the pituitary gland. It therefore becomes evident that further study is required completely to elucidate these problems.

Inanition: Generally in starvation the testes of the young fail to develop in regard to both spermatogenic and androgenic properties. Except in extreme conditions of starvation, the spermatogonia remain normal in appearance and apparently in function. The spermatocytes, however, undergo complete degeneration. Unless vitamin E deficiency exists, a return to normal occurs if the animal is placed on an adequate diet.

In the adult, some loss of weight can occur without testicular injury. However, severe weight loss results in a return of the testes to a condition similar to the prepuberal state. The germinal epithelium continues to proliferate but the germ cells fail to mature. The interstitial elements appear normal, but do not secrete the usual amount of male sex hormone. These changes can at least partially be attributed to failure of the pituitary gland adequately to stimulate the testes. The adult testis recovers readily from the effects of inanition when the cause is removed.

ACCESSORY SEX GLANDS

From the endocrinologic standpoint, the secondary sex glands of the male are dependent upon the testes. Under normal conditions their activity is controlled by the amount of androgen available. Dietary deficiencies not only alter the amount of androgen available, but also have a direct effect upon the secondary sex glands. These glands are lined with an epithelial membrane. They are therefore susceptible to keratinization in vitamin A deficiency. Such keratinization has been reported in the glandular structures as well as in the epididymis and vas deferens. Infection of these structures probably occurs more readily under these circumstances. Also, the filling and stoppage of the efferent ducts with cell debris probably seriously interferes with their function.

Vitamin A has a marked growth promoting effect. In its absence the secondary sex glands become atrophic. This atrophy results from testicular failure, as evidenced by the fact that testicular stimulation by gonadotropic substances will restore the glands to the normal state. Similarly, in vitamin B deficiency, it appears that the pituitary-testis mechanism is responsible for the atrophy of the secondary sex glands. If the testes are stimulated to produce androgens, the seminal vesicles and prostate do not show pathologic changes.

Vitamins C, D and E have little, if any, influence on the secondary sex glands.

THE OVARIES

As with the testes, the ovaries are functionally reciprocally related to the pituitary gland. Ovulation and the production of ovarian hormones (estrogens and progesterone) occur as the result of pituitary stimulation. The gonadotropic activity of the pituitary, in turn, is governed to a considerable extent by ovarian hormones. Thus, in many respects, the ovaries are analogous to the testes. Their reaction to vitamin deficiency, however, is quite different in that they are much less susceptible than are the testes to nutritional deficiency.

Deficiencies of vitamins A, B, C, D, and E seem to have no direct effect upon the ovaries. Whenever functional or morphologic changes occur in the ovaries because of nutritional disturbances, these changes probably are due to anorexia and cachexia resulting in malnutrition, decreased production of sex hormones by the pituitary gland and, in turn, by the ovaries.

As in the case of the male, there is considerable evidence to demonstrate a relationship between the female gonads and calcium metabolism. The close chemical relationship between the sex hormones and vitamin D has been pointed out. Whether or not it is this similarity that results in effects on calcium metabolism is not known.

Although the ovary is singularly resistant to vitamin deficiencies, it is peculiarly susceptible to inanition. In young animals, starvation causes marked retardation of sexual development with failure of follicular maturation. In the adult in all mammals studied, ovulation is repressed by a degree of inanition which has little effect upon spermatogenesis. Cessation of cyclic activity and sterility occurs during periods of starvation.

THE UTERUS AND VAGINA

The development of the vagina and uterus, and the cyclic changes which occur in the vaginal epithelium and in the endometrium are influenced by estrogens and progesterone which are products of the ovaries. These organs are, however, more sensitive to vitamin A deficiency than is the ovary. The epithelial keratinization which occurs in vitamin A deficiency is observed in both the uterus and the vagina. In the uterus this may cause increased susceptibility to infection and decreased fertility. The latter may be the result of difficulty in the ascent of the sperm or of improper conditions for nidation.

In vitamin A deficiency the keratinization of the vaginal epithelium results in the appearance of cornified epithelial cells in the vaginal smears. Such a smear could be misinterpreted as indicating continuous estrous resulting from estrogenic stimulation. This is clearly not the case, since it occurs also in oöphorectomized animals. The vagina responds very rapidly to vitamin therapy and becomes normal in the course of a few days. Hypervitaminosis-A has been observed to produce vaginal symptoms characterized by a prolonged period of di-estrous, during which there is failure of epithelial cornification.

None of the other vitamins have been demonstrated to cause a direct effect on the vagina or the nongravid uterus. As will be shown, vitamin E influences gestation, and any factor (e.g. vitamin B deficiency) which produces inanition may indirectly effect these organs. The atrophy and degeneration which occurs in all the tissues of the vagina and uterus during starvation are readily reparable by dietary measures.

GESTATION

The epithelial changes induced in the uterus in the vitamin A-deficient animal results in serious impairment of reproductive function. As stated by Mason[2], "pregnancy usually culminates in variable degrees of fetal resorption, late fetal death, extended gestation, prolonged and difficult parturition, frequent stillbirth, and high mortality of the viable offspring." None of these reproductive defects appears to be the result of any interference with the hormonal mechanisms involved. In every instance, the gestational failure seems to be caused by the pathologic changes in the epithelial tissues which results in failure of proper function or increased susceptibility to infection.

It has already been pointed out that pituitary-gonadal function is greatly depressed during vitamin B deficiency, and that the effect of hypovitaminosis-B on the reproductive system is probably nonspecific and is the result of inanition. These statements also apply to the influence of vitamin B deficiency during gestation. Dead or puny offspring frequently result. The fetus usually is small, which may reflect the absence of growth hormone. In severe deficiency resorption of the fetus or abortion may occur. Sometimes frank beriberi may occur during gestation because of added requirements for thiamin. In this connection it might be mentioned that during lactation thiamin requirements are very high, and that as a result vitamin B_1 deficiency may readily result if the diet is not consistently high in that vitamin.

Vitamin C deficiency will interrupt pregnancy or result in the birth of offspring with scorbutic tissues. Some investigators believe that during pregnancy the symptoms of scurvy are relieved somewhat. Whether

or not this is due to a metabolic change or to vitamin production by the fetus has not been determined.

The reproductive capacity is retained in an amazingly normal fashion in vitamin D deficiency. The fetus is less apt to show rickets than the mother to have osteomalacia.

The female rat on a vitamin E free diet shows no demonstrable changes in reproductive capacity until after the onset of pregnancy. Pregnancy is terminated by the uterine resorption of the fetuses. The pathology of the process has been studied in detail and is unique. It consists essentially in a failure to establish adequate fetal circulation through the placenta. Considerable evidence indicates that vitamin E is essential in most mammals. In the human it may play some role involving the metabolism of the estrogens during pregnancy. It has been reported to be of value in spontaneous abortion.

CONCLUSION

In considering the physiology or pathology of the reproductive organs, it is clear that the normal endocrinologic control can seriously be disturbed by numerous nutritional deficiencies.

REFERENCES

1. Bernheim, F.: Interaction of vitamins and drugs with cell catalysts, J. Lab. & Clin. Med. 26:20-30 (October) 1940.

2. Mason, K. E.: Chapter XXII, Sex and Internal Secretions, 2 ed., by E. Allen, Baltimore, Williams & Wilkins, 1939.

ANGINA PECTORIS WITH PAIN OF ATYPICAL DISTRIBUTION

Report of a Case Illustrating the Diagnostic Value of Electro-Cardiographic Changes During an Induced Attack of Pain

W. L. PROUDFIT, M.D. and A. CARLTON ERNSTENE, M.D.

An occasional patient with angina pectoris caused by coronary artery disease suffers from pain of such atypical distribution that, in order to establish the diagnosis beyond doubt, it becomes important to obtain objective evidence of organic heart disease. The electrocardiogram taken at rest furnishes the desired information in some of these patients, but in a considerable number no significant electrocardiographic changes are present. In the latter group, an electrocardiogram taken during an induced attack of pain usually shows changes in the S-T segment or the T wave of greater degree than occur in the tracings of normal individuals after the same amount of exercise. The value of these changes as a corroborative diagnostic measure is demonstrated in the following case report.

REPORT OF CASE

A businessman, 56 years of age, came to the Clinic because of attacks of stiffness in the neck and "congestion" in the substernal region. The symptoms had appeared first eighteen months earlier, and during the last seven weeks had become much worse. Both the stiffness in the neck and the sense of congestion in the chest were induced by exertion. The patient was unable to walk more than half a city block at a moderate pace without experiencing such distress that he would find it necessary to stop. With rest the symptoms would subside in about ten minutes. Exposure to cold air appeared to be an important predisposing factor in the development of the attacks and, at times, the symptoms were brought on by smoking. The relief afforded by rest seemed to be hastened by the inhalation of spirits of ammonia, by taking nitroglycerine, or by drinking a small amount of whiskey. Digitalis had been taken for short periods during the seven weeks before his admission, without benefit.

The attacks began with a choking sensation in the throat, followed immediately by a sensation of aching and stiffness in the back of the neck. The aching radiated into the occipital region and sometimes into the shoulders and outer aspect of both arms as far as the elbows. The discomfort in the neck was followed shortly by the development of a sense of fulness in the substernal region, which was accompanied by moderate dyspnea.

Physical examination revealed a well developed and well nourished middle-aged man. The pulse rate was 63 per minute and the blood pressure, 100 mm. systolic and 68 mm. diastolic. There was slight tenderness over the lower cervical spine. The lungs were clear throughout. The heart was not enlarged, its rhythm was regular, but the sounds were of poor quality. No murmurs were heard. There was moderate sclerosis of the peripheral arteries.

A clinical diagnosis of coronary heart disease with angina pectoris was made. It was thought that degenerative arthritis of the cervical spine may have been a factor in determining the atypical distribution of the anginal pain.

The blood count and urinalysis gave findings within the limits of normal. The Wassermann reaction of the blood was negative. Roentgenologic examination of the chest showed the heart to be normal in size, shape, and position, and the lung fields to be clear. Examination of the cervical spine revealed ankylosis of the fifth and sixth cervical vertebrae, apparently a congenital defect. The electrocardiogram showed sinus rhythm with a rate of 62, slight sagging of the S-T segments in Leads II and III, diphasic T waves in Lead II and inverted T waves in Lead III.

An exercise tolerance test was done by having the patient mount and descend a two-step staircase. An electrocardiogram was taken before beginning the exercise, and the electrodes were kept in place throughout the test. Fifty trips over the steps failed to induce distress in the neck or chest. Immediately after cessation of the exercise, Lead IV_F of the electrocardiogram was recorded. The patient then was given several ice cubes to hold in his left hand while exercising on the steps once more[1]. After ten trips he began to experience a choking sensation in the throat but no aching in the neck or substernal oppression. In spite of about fifteen additional trips over the steps, no further sensations developed, and at that time the exercise was terminated. Lead IV_F was recorded immediately. About three minutes after the cessation of the test, the patient began to complain of severe substernal oppression and was in obvious distress. Lead IV_F was recorded again, and the patient was given a tablet of nitroglycerine, grains 1/100, which promptly gave relief from all symptoms. The patient had noted only a little aching in the back of the neck when he had the substernal distress. A 4-lead electrocardiogram was taken about three hours later.

Figure 1 shows the electrocardiogram taken at rest. Since the patient had had an unknown amount of digitalis during the previous seven weeks, the changes in the S-T segments and T waves are of doubtful significance. Figure 2 shows the effect of exercise on Lead IV_F. Tracing A is the normal control. It shows 0.8 mm. depression of the S-T segment and a T wave 4 mm. in height. Tracing B, taken after fifty trips over the steps, shows 1.0 mm. depression of the S-T segment and a T wave 5 mm. in height. Tracing C, taken after twenty-five additional trips over the steps while ice was being held in the left hand, shows 1.0 mm. depression of the S-T segment and a T wave 5 mm. in height. Tracing D, taken after the onset of the pain in the chest, shows the S-T segment to be depressed 4.5 mm. and the T wave to be 10 mm. in height. Bradycardia appeared with the onset of the substernal pain. The electrocardiogram taken three hours after the exercise tolerance test was identical with the control tracing.

DISCUSSION

The changes in the electrocardiogram during and after attacks of angina pectoris induced by exercise have been studied by a number of observers and were recently investigated under standardized conditions by Riseman, Waller and Brown[2]. Riseman and his associates observed a deviation, usually a depression, in the level of the S-T segment of Lead IV in all of twenty patients during an induced attack of pain. They also demonstrated that similar changes occur in normal individuals after a measured amount of exertion but, in general, the deviation in normal persons is of less magnitude than in patients who have angina pectoris. Changes in the level of the S-T segment of 1.5 mm. or more were encountered commonly during attacks of angina pectoris, but deviations of this degree were not recorded in any of the normal individuals. When, however, the electrocardiographic changes in patients with angina pectoris, after an amount of exercise which seldom caused pain, were compared with the changes in normal individuals after the

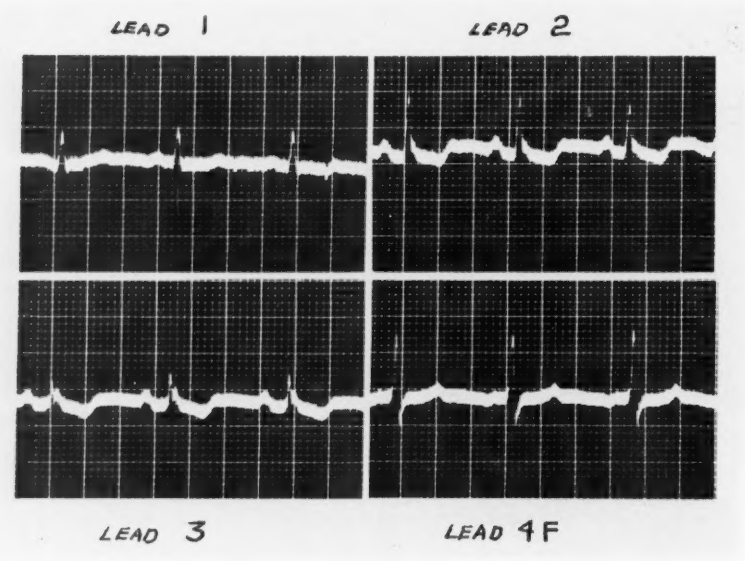


Figure 1. Electrocardiogram taken at rest.

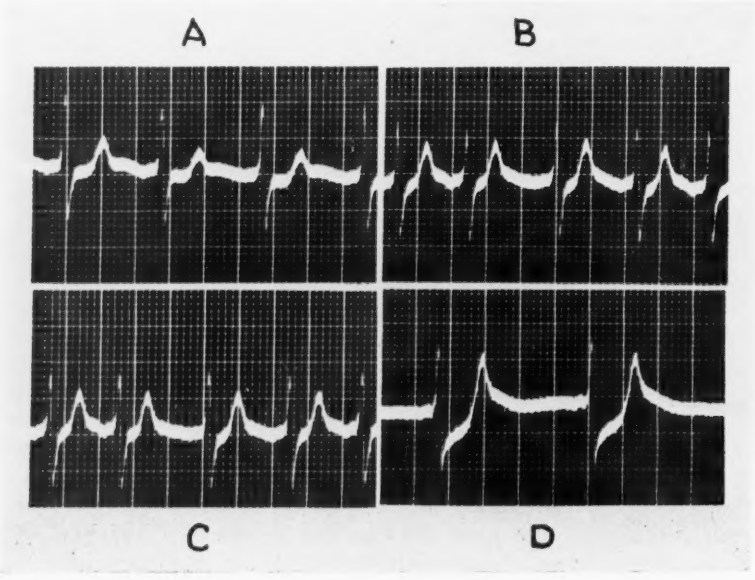


Figure 2. The effect of exercise on Lead IVF of the electrocardiogram. A., at rest; B., after 50 trips over two-step staircase; C., after 25 additional trips with ice in left hand; D., 3 minutes after C.

same amount of exertion, the differences between the two groups were not sufficient to be of diagnostic value. It is our opinion, however, that when the patient's pain is reproduced by exercise and the electrocardiogram taken during the attack shows a striking change in the level of the S-T segment, this combination is a valuable aid in diagnosis. Of course, this procedure is not necessary in patients who have typical angina pectoris, but it may be of great diagnostic help in individuals who have anginal pain of atypical distribution. In the case reported in the present communication, the patient's pain was induced by exercise, and the magnitude of the depression of the S-T segment in Lead IV of the electrocardiogram furnished important additional evidence of the cardiac origin of the distress.

Riseman, Waller and Brown[2] observed that changes in voltage of the T wave, either an increase or a decrease in amplitude, commonly occur during or after attacks of angina pectoris. A decrease in the voltage of the T wave also was induced by exercise in normal individuals, but an increase in amplitude was not recorded in any of fifteen normal persons. In the case reported above there was an increase of 6 mm. in the amplitude of T_4 during the attack.

Roentgenologic examination of the cervical spine revealed fusion of the bodies of the fifth and sixth cervical vertebrae, and this may have been an important factor in determining the location of the initial symptoms of the patient's attacks. Boas and Levy[3] are of the opinion that extracardiac disease often determines the location and radiation of anginal pain.

SUMMARY

A case of angina pectoris is reported in which the attacks began with a choking sensation in the throat followed immediately by a sensation of aching and stiffness in the back of the neck. It is believed that the presence of ankylosis of the fifth and sixth cervical vertebrae was an important factor in determining the location of the initial symptoms of the attacks. Electrocardiograms taken during an attack induced by exercise showed marked depression of the S-T segment and an increase of 6 mm. in the amplitude of the T wave in Lead IV_F. The electrocardiographic changes were of value in corroborating the clinical diagnosis of angina pectoris.

REFERENCES

1. Freedberg, A. S., Spiegl, E. D. and Riseman, J. E. F.: Studies on the effect of cold and heat in patients with angina pectoris. (Proc. Soc. Clin. Invest.), J. Clin. Invest. 20:459 (July) 1941.
2. Riseman, J. E. F., Waller, J. V. and Brown, M. G.: Electrocardiogram during attacks of angina pectoris; its characteristics and diagnostic significance, Am. Heart J., 19:683-707 (June) 1940.
3. Boas, E. P. and Levy, H.: Extracardiac determinants of the site and radiation of pain in angina pectoris with special reference to shoulder pain, Am. Heart J. 14:540-554 (November) 1937.

The Frank E. Bunts Institute

The Frank E. Bunts Institute will present a course in Progress in Therapy on Monday and Tuesday, December 1 and 2, 1941.

The program of the course and an application blank will be found on succeeding pages of this Quarterly.

★

Program

PROGRESS IN THERAPY

Monday, December 1, 1941

8:30 A.M.—Registration

9:00 A.M.—Differential Diagnosis of Bone Tumors.....B. H. Nichols, M.D.

9:30 A.M.—The Malignant Prostate.....Wm. E. Lower, M.D.

10:00 A.M.—Differential Diagnosis and Treatment of Undulant Fever.....C. L. Hartsock, M.D.

10:30 A.M.—Newer Concepts of Low Back Pain.....J. A. Dickson, M.D.

11:00 A.M.—Spot Films in Gastrointestinal X-ray.....J. C. Root, M.D.

11:30 A.M.—Special Lenses for the Poor Sighted.....R. J. Kennedy, M.D.

11:45 A.M.—The Chronic Running Ear.....P. M. Moore, Jr., M.D.

12:00 A.M.—The Indications and Contraindications for the Use of Fever Therapy in Central Nervous System Syphilis.....E. W. Netherton, M.D.

12:30 P.M.—Lunch

1:00 P.M.—The Modern Interpretation of Diseases of Civilized Man.....G. W. Crile, M.D.

1:30 P.M.—Modern Therapy in Cardiac Disease.....A. C. Ernstene, M.D.

2:00 P.M.—The Applied Physiology of Bile Secretion and Bile Salt Therapy.....A. C. Ivy, M.D., Professor of Physiology and Pharmacology, Northwestern University Medical School

3:00 P.M.—End Results in Treatment of Ulcer with Aluminum Hydroxide.....E. N. Collins, M.D.

3:30 P.M.—Improved Methods in Fracture Treatment....J. I. Kendrick, M.D.

4:00 P.M.—Chemotherapy in Surgery.....George Crile, Jr., M.D.

4:30 P.M.—Newer Concepts in the Management of Prostatic Obstruction.....W. J. Engel, M.D.

5:00 P.M.—Laryngo-Tracheal Bronchitis in Children.....Justin M. Waugh, M D.

6:00 P.M.—Dinner

8:00 P.M.—Frank E. Bunts Lecture.
The Rationale of the Treatment of Hepatic Disease.....A. C. Ivy, M.D., Professor of Physiology and Pharmacology, Northwestern University Medical School

Tuesday, December 2, 1941

8:00 A.M.—Clinical-Pathological Conference	Allen Graham, M.D., Russell L. Haden, M.D., and others
9:00 A.M.—Surgical Treatment of Ruptured Intervertebral Disc	W. J. Gardner, M.D.
9:30 A.M.—Progress in the Therapy of Renal Disease	R. H. McDonald, M.D.
10:00 A.M.—The Management of the Poor Risk Goiter Patient	R. S. Dinsmore, M.D.
10:30 A.M.—Use of Chemotherapy in Urinary Tract Infections	C. C. Higgins, M.D.
11:00 A.M.—Advances in Allergy	C. R. K. Johnston, M.D.
11:30 A.M.—Recent Development in Use of Testicular Hormones	E. P. McCullagh, M.D.
12:00 A.M.—Recent Advances in Roentgen Therapy	U. V. Portman, M.D.
12:30 P.M.—Lunch	
1:30 P.M.—Nonspecific Therapy	John Tucker, M.D.
2:00 P.M.—Methods of Treatment in Peripheral Vascular Disease	W. J. Zeiter, M.D.
2:30 P.M.—Treatment of Vestibular Vertigo	H. E. Harris, M.D.
2:45 P.M.—Recent Progress in Treatment of Primary Lung Tumors	H. S. VanOrdstrand, M.D
3:15 P.M.—Advances in Myelography	Wm. A. Nosik, M.D.
3:30 P.M.—Progress in Treatment of Tumors of the Nervous System	A. T. Bunts, M.D.
4:00 P.M.—Treatment of Complicated Diabetes	E. J. Ryan, M.D.
4:30 P.M.—Differential Diagnosis and Treatment of Acne	Geo. H. Curtis, M.D.
4:45 P.M.—Therapy of the Blood Dyscrasias	Russell L. Haden, M.D.

REGISTRATION BLANK

....., 1941

The Frank E. Bunts Institute
Cleveland Clinic
Cleveland, Ohio

Gentlemen:

Please register me for the course in "Progress in Therapy" which is to be given December 1 and 2, 1941.

I am enclosing a check for $5.00, and the remainder of the fee, $5.00, will be paid on registration, December 1.

Name.....

Address.....

.....
Medical School from which Graduated

Note: Checks should be made payable to The Frank E. Bunts Institute and sent to A. D. Ruedemann, M.D., Cleveland Clinic, Cleveland, Ohio.

CONTRIBUTORS

INDEX